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# Drug delivery systems for targeting the blood-brain barrier for the treatment of malignant brain tumor: Current status and prospects of drug delivery approaches with Pathological point

**Bahareh Fazeli[1], Zahra Khalili[2], Mohammad Deilami[3], Raheleh Tavakolimoghadam[4], Amin Rostami[5]***

[1.]Department of clinical pharmacy,Faculty of pharmacy,Tehran medical sciences, Islamic Azad university, Tehran, Iran

[2.]Master of Midwifery Consultation, Zahedan University of Medical Sciences, Zahedan, Iran

[3.]MD,Department of Anesthesia, School of medicine, Iran university of medical sciences, Tehran, Iran

[4.]Anatomical and clinical pathologist,Bahar pathobiology Laboratory,Tehran,Iran

[5.]chief Resident of Neurosurgery,Department of neurosuegery, Faculty of medicine, mashhad university of medical sciences, mashhad, Iran

## Abstract

Brain tumors are defined as primary intracranial tumors in the brain. These tumors account for 1.8% of newly diagnosed cancers and 2.3% of cancer-related deaths worldwide. The purpose of the present study is to investigate drug delivery systems to target the blood-brain barrier for the treatment of malignant brain tumors: current status and prospects of drug delivery approaches.

Materials and methods: This research was a clinical trial that was conducted in 1402 at the Imam Khomeini educational-therapeutic center in Tehran. The statistical population of the study was made up of patients with brain malignancy who referred to the mentioned centers. The procedure was that after obtaining the approval of the medical ethics committee of Tehran University of Medical Sciences, 60 patients with brain cancer were selected and randomly assigned. They were divided into two groups of 30 people. The first group underwent new treatments for malignancy according to the stage of disease progression. The second group includes patients who used old treatment methods to treat malignancy. Finally, the obtained data were analyzed using t-test, 2 Mann-Whitney and repeated measures ANOVA in SPSS software version 24 (version 24, IBM Corporation, Armonk, NY).

Conclusion: It is important to pay attention to the structural features of the blood-brain barrier and the way of intercellular transmission, as well as to choose the appropriate drug and drug delivery system for the targeted and systematic treatment of central nervous system diseases. has been Also, drug delivery systems based on nanoparticles and the most important nanocarrier structures including biopolymer nanoparticles, nanoliposomes, dendrimers and solid lipid nanoparticles have been investigated.

**Key words:** Drug delivery system, blood brain barrier, brain cancer.

## Introduction

Cancer is a complex multifactorial disease that is the result of cells leaving the correct regulatory, proliferation and differentiation pathways, and among the factors that lead to its malignancy are insensitivity to growth inhibitory signals, avoidance of programmed cell death, tissue invasion and metastasis (1). In the current era, cancer is one of the hottest topics in the field of cellular and molecular biology, and so far many studies have been conducted on its molecular mechanisms and many mechanisms have been identified. Not achieved Brain tumors are defined as primary intracranial tumors in the brain (2). These tumors account for 1.8% of newly diagnosed cancers and 2.3% of cancer-related deaths worldwide.Glioma is the most common type of brain cancer, and its significant variation between tumor and intratumor makes its diagnosis challenging (3). The most diverse and incurable subtype of glioma is glioblastoma multiforme, which has been chosen as a key target in biological research due to its severity and high mortality rate (4). Advances in understanding the molecular causes of glioma have improved the classification of brain tumors. Also, the expansion of knowledge in medical genetics and epigenetics also helps to better understand the molecular disorders of glioma.Brain tumors include a wide range from benign pilocytic astrocytoma (Astrocytoma pilocitico) to highly malignant and progressive glioblastoma multiforme (5). Compared with metastatic brain tumors that arise from other organs and tissues, primary brain tumors such as glioma are originally from cells They originate from the brain (0.2). The most common location of glioblastoma tumor is within the brain tissue and due to the high migration ability of these cells, it is considered one of the most malignant brain cancers (6). This tumor has the worst prognosis and clinical results, and despite the integration of different strategies The treatment which includes surgery, radiotherapy and chemotherapy, the average life span of affected patients is around 0.02 to 0.00 months (0 and 3). The treatment of this disease faces many challenges and despite the available treatment methods, the



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neurotoxicity of these methods is also a challenge (7). It is considered great in the treatment of this disease .Inventing new methods of drug delivery to prevent the systemic toxicity of these drugs, as well as the targeted delivery of drugs to the tumor site, are among the new approaches that are considered by researchers today (8). The use of stem cells as a carrier in the treatment of cancers is one of these treatment methods. But the use of these cells due to their low acceptance at the transplant site, ethical problems of their preparation and isolation, immunological obstacles, transplant rejection, as well as risks and concerns about tumor formation by these cells, has opened a new chapter in cell therapy research using products (9). Stem cells are among exosomes. Immunotherapy is one of the things that prevent tumor. Immunotherapy has two main strategies (active or passive) to activate the immune system. Active strategies that are aimed at creating immune responses and anti-tumor movements with specific antigens so that they can ultimately cause effective treatments for cancers, immune disorders or diseases (10). But In passive strategies, specific characteristics of tumor biology are used, which include tumor targeting by carrier nanoparticles (using tumor cells with high permeability), which have high penetration and survival capabilities. In the middle of the 9th decade, passively target carrier nanoparticles reached the level of clinical trials and the first products based on liposomes and polymer and protein proteins were released to the market in the mid of the 9th decade (11). Later, therapeutic nanocarriers based on this strategy entered the field and were approved for wider use and faster treatment, and more methods were added to this strategy and investigated to target drugs to cancer cells (12). Among the drug delivery systems based on nanotechnology, we can mention all kinds of synthetic nanoparticles and biological vesicles that have biological properties for the treatment of the target area in vivo (13). In recent years, several synthetic nanoparticles have been used as vesicles to deliver therapeutic drugs to the bulk of the tumor and directly affect the target site. One of the most important aspects of drug and vaccine production and design that should be taken into consideration is effective drug and vaccine delivery systems without any harm or side effects to the body (14). Therefore, a delivery system should be examined in every aspect and its advantages and disadvantages should be compared with other delivery systems in order to choose the best delivery system for the drug or vaccine. In the case of the vaccine, the antigen delivery system should be able to quickly stimulate the humoral and cellular immune system and create a strong and stable immunity against the pathogen (15). In the case of medicine, the delivery system must be able to deliver the medicine to the desired place in the body. So far, many drug and vaccine delivery systems have been tested and used. Recently, the use of polymer nanoparticles, liposomes and their components such as transferosomes, autosomes, ethosomes, niosomes, and marinosomes have been used. ), dendrimers, lipid nanocarriers, solid polymer micelles, nanocapsules, nanoemulsions, ceramic nanoparticles, metal nanoparticles (such as iron oxide, gold, silver, gadolinium and nickel and carbon nanomaterials including nanotubes and fullerenes) ) have been taken into consideration for the transfer and delivery of drugs (16). The advantages of these nanoparticles can be mentioned in their small size, preventing the drug or vaccine from disintegrating and releasing the drug over long periods of time, targeted transfer of the drug or vaccine, but these nanoparticles Particles have disadvantages such as toxicity, non-degradability, accumulation in the body and causing inflammation. Among the nano drug delivery systems in the world market, some cases can be mentioned (17). A drug with the brand name Adagen has a polymer nano particle structure containing the active ingredient adenosine. It is a deaminase that is used in patients with adenosine deaminase enzyme deficiency (18). The drug Ambisome containing amphotericin B is used to treat fungal infection and the drug Myocet containing doxorubicin is used to treat advanced breast cancer, which are liposomal nanoparticles (19). Among all biological barriers, the blood barrier The brain is considered a strong barrier for the transfer of drugs to the brain. This barrier is a semi-permeable barrier against harmful chemicals as well as harmful substances in the bloodstream, and it plays a role in regulating the entry of nutrients into the brain for its proper functioning (20). Astrocytes are composed of endothelial cells, neurons, and basement membrane. The development of targeted drug delivery systems is necessary for the treatment of neurological diseases. With the expansion of nanotechnology and nanomedicines, new methods with the help of nanotechniques for the targeted treatment of various diseases, including neurological diseases, have been reported in various studies. These targeted drug delivery systems have increased the efficiency and effectiveness of drugs (21).



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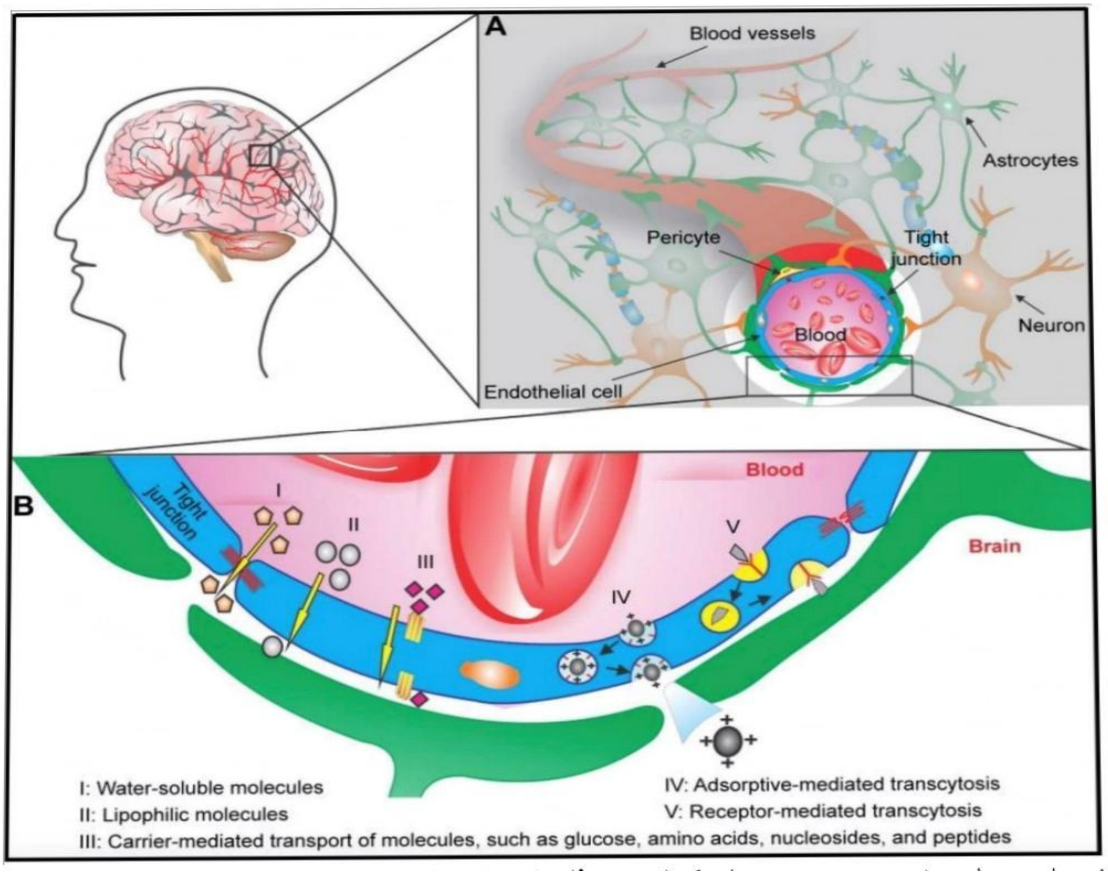



Figure 1- Channels for passing through the blood-brain barrier in the blood vessel wall (the cross-section of the cerebral capillary and the structure of the blood-brain barrier, which has a network of pericytes, neurons, astrocytes, and endothelial cells) They enter the blood-brain barrier in water (1) Fat-soluble molecules are dispersed on endothelial cells. (II) Carrier-mediated transport for the transport of small molecules and peptides (III), improvement of the transcytosis method by drug-assisted absorption (17) passage of larger molecules through receptor-mediated transcytosis (1)

## Materials and methods

This research was a clinical trial that was conducted in 1402 at the Imam Khomeini educational-therapeutic center in Tehran. The statistical population of the study was made up of patients with brain malignancy who referred to the mentioned centers. The inclusion criteria included brain cancer patients, absence of systemic diseases such as diabetes, absence of history of central nervous system diseases, informed consent of the individual to participate in the research. In addition, it was decided that if the patient does not return 3 and 6 months after the treatment, the patient will be excluded from the study. Also, during the initial investigation, patients who were in the final stages of brain cancer were excluded from the study due to the possibility of their death. The procedure was as follows: after obtaining the approval of the medical ethics committee of Tehran University of Medical Sciences, 60 patients with brain cancer were selected and randomly divided into two groups of 30 people. They were placed with the progress stage of the disease. The second group includes patients who used old treatment methods to treat malignancy. Finally, the obtained data were analyzed using t-test, 2 Mann-Whitney and repeated measures ANOVA in SPSS software version 24 (version 24, IBM Corporation, Armonk, NY).

## Discuss

Nanoparticles have drug-releasing properties that create a high concentration of related drugs around the tumor and increase anti-cancer efficiency . Exosomes are among the factors that we have witnessed its progress. Which are used as nanovesicles for gene transfer and drug therapy (5). Exosomes are 31- to 11-nm endosomal vesicles first described by Trams et al. And then by Johnston and his colleagues in 1977, it was confirmed that high levels of transfer protein attached to small particles (exosomes) were observed, and they showed that reticulocytes by eliminating unnecessary proteins (especially transfer receptors) through Exosome release

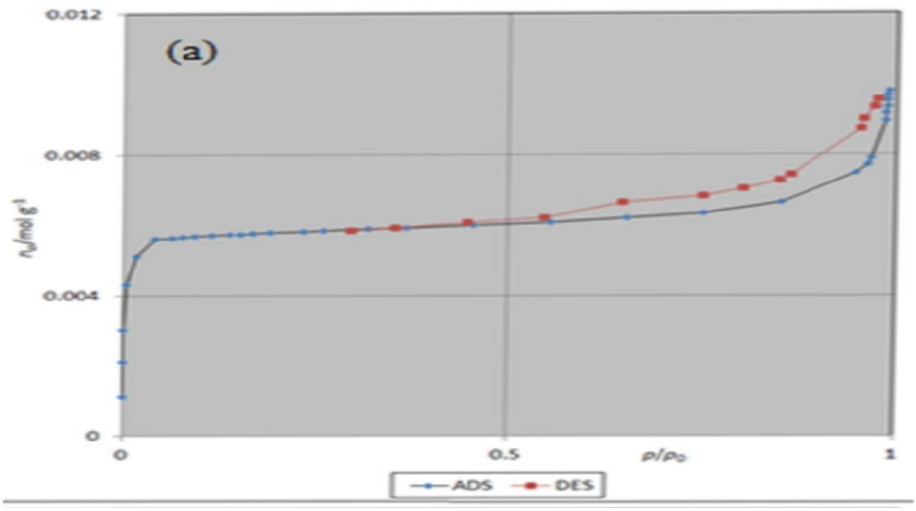
matures into erythrocytes (3). In general, these exosomes are released by all types of mammalian cells to the extracellular environment in both pathological and physiological conditions (11).

| Nanocarriers | Medicinal composition | Target site | Type of disease |
|---|---|---|---|
| Polymer–protein conjugate | Hedgehog pathway inhibitor (HPI | ALDH, CD133 | Brain tumor |
| liposomes | F3 peptide, γ-secretase inhibitors (GSIs), Tamoxifen, Paclitaxel | Nucleolin, CD44 | Paclitaxel Triple negative breast cancer (TNBC) |
| niosomes | 5′-fluorouracil | H3K9 | colorectal, head neck, esophageal, and gastric cancers |
| micelles | phenformin, gemcitabine, thioridazine | ALDH1A1, CD44 | Breast cancer, lung cancer |
| albumin-bound paclitaxel nanoparticles | Paclitaxel | Nucleolin, CD44 | breast cancer |
| Radio-immunoconjugate | iodine 131–tositumomab | CD20 | non-Hodgkin's lymphoma |
| Gold nanoparticles | Doxorubicin | TGF-β, acid-labile hydrazone bond | Breast cancer |

Membranes without eukaryotic content (the so-called ghost) have high biological and biocompatibility capabilities and are non-toxic, non-stimulating and have a long life in the blood circulation, but unfortunately, their capacity to load drugs is limited and the shape change during transportation is often It causes unstable blockage and material leakage, which limits clinical use (12). However, exosomes are secreted from living cells, and have characteristics such as biocompatibility, non-cytotoxicity, low immunogenicity, easy production, long shelf life, and high loading capacity (16).

Chate 1: Drug absorption and reabsorption in the blood-brain barrier

Exosomes have unique abilities to transport RNA and proteins. They are important mediators of intercellular communication and cellular regulators, and their altered characteristics in many diseases, such as cancer, indicate that exosomes are useful targets. diagnostic and therapeutic importance (11). In recent decades, various researches have been done to understand exosome behaviors and their ability to deliver drugs. To improve the



exosome drug delivery system, various manipulations on natural exosomes, especially on a new class of exosomes It has been done (22-33).

| medicine name | Percent Drug loading | Percent drug release (pH: 7/4) | P-value |
|---|---|---|---|
| Doxorubicin | 50 ٪ | 32 ٪ | 0/05 |
| Ciprofloxacin | 93 ٪ | 74 ٪ | 0/043 |
| Ciprofloxacin | 42 ٪ | 38 ٪ | 0/011 |
| Nigella sativa | 88 ٪ | 50 ٪ | 0/054 |
| Tetracycline | 95 ٪ | 70 ٪ | 0/065 |

**Table 1: Drug loading and release**

## Conclusion

According to the stated content, it can be concluded that the use of nanotechnology in order to increase drug delivery to the brain by crossing the blood-brain barrier without destroying it can be promising in the field of treating neurological diseases. Production of nano-scale structures for treatment Diseases of the central nervous system is a challenging task because in the design of a drug delivery system in the structure and nanoscale, the necessary conditions for compatibility with the brain tissue, such as biocompatibility, biodegradability, the biology of drug release, accurate pharmacokinetics and pharmacodynamics, maximum therapeutic effects and minimum side effects must be met. The side should be considered. Recent advances in molecular cell biology and the effective expansion of new medical technologies show a fundamental understanding of the barriers of the central nervous system with special emphasis on the blood-brain barrier, which represents the inherent protective structures of the human brain against internal and external molecules, especially drugs.Recently, the trend of cancer treatment has shifted towards the design of stable and safe biological delivery systems compatible with humans. The use of exosomes as an efficient and non-toxic drug opens a new window for cancer treatment. The field of brexosome-based drug delivery has grown tremendously, and our understanding of applications may have advanced greatly over the past few years. Many studies have highlighted the necessary conditions under which exosomes can act as therapeutic carriers. In particular, cancer seems to be a suitable study for exosome-based drug delivery systems, which has been reflected in many cancer-related studies. To improve this system, biotechnological methods have been used to design a powerful immune-stimulating drug delivery system that can recognize its target. The new technology allows the engineering of large-scale exosome-based delivery systems that are used in medical applications. In general, more studies are needed to address the challenges in designing an effective delivery system.

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