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NANOTECHNOLOGY FOR SPECIFIC DRUG ADMINISTRATION

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ABSTRACT

In the past ten years, nanotechnology has significantly addressed a number of nanomaterials in the biomedical field, offering the chance to obtain more effective therapy, more targeted distribution, and an enhanced safety profile. During drug distribution, nanocarriers may be able to shield the active chemical. The delivery of medications and genes has improved the molecule's bioavailability at the illness site and provided good control over the molecule's release, depending on the nanosystem being used. This chapter covers a variety of cutting-edge nanomaterials intended to create improved nanocarrier systems for treating ailments like malaria, heart failure and cancer. Additionally, we show how promising nanocarriers are for facilitating biodistribution and diagnostic ease for effective clinical cancer therapy.

KEYWORDS

Nanotechnology, Nanocarriers, Drug distribution and Nanomaterials.

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INTRODUCTION

By applying nanotechnology to enhance pharmaceuticals and healthcare, nanomedicine creates a new field that holds promise for the twenty-first century[1,2]. By identifying the location of human disease, nanomedicine can target biological cells with drugs, diagnostics, and treatments. The diagnosis was first based on the idea of cell theory, but atomic and molecular levels of inquiry have since been reached[3]. As a result, the nanoscale size gives materials additional characteristics including structure, form, and large surface area, which enhance its forms for therapy and diagnosis[4,5]. Therefore, delivering the desired molecules to their target areas while reducing adverse effects and optimizing therapeutic effects is

the primary goal of nanomaterials in delivery applications[6,7]. Nanomaterials are essential to drug delivery systems because they enhance the solubility and stability of pharmaceuticals, regulate their release, reduce their toxicity, and enhance their therapeutic benefits[8]. Numerous nanocarrier systems, including polymeric, inorganic, and nanohydrogel nanoparticles, have been produced[9]. It's also crucial to comprehend how they interact with specific cells, how they are administered, how bioavailable they are, and how they are distributed[10,11]. Conversely, gene delivery presents novel approaches to illness treatment by the introduction of new genetic materials into cells through *ex vivo* and/or *in vivo* administrations[12]. Using lipids and calcium phosphate, various vectors transmit DNA chemical transduction and transfection, ensuring the gene-transferring process[13]. Generally speaking, these systems are more advantageous when treating various illnesses, particularly cancer, which is predicted to be the second biggest cause of death globally in 2020, behind heart disease, which accounts for almost 10 million deaths or one in six deaths. (WHO; 2022). Furthermore, according to[14], their successful research demonstrated protection against a number of viral illnesses, including the coronavirus, the Ebola virus, and malaria. Furthermore, a number of studies demonstrated their efficacy in delivering large doses of medicinal drugs, biodegradability, safety, non-viral techniques and diversity of structural conformations[15,10].

SPECIFIC DRUG ADMINISTRATION

In addition to the adverse effects of the delivered pharmaceuticals, the use of big sized materials in drug delivery presents a number of difficulties, such as low bioavailability/solubility/absorption, problems with target-specific distribution and poor *in vivo* stability. Consequently, utilizing novel drug delivery techniques to concentrate medication in a particular part of the body may present a chance to address these pressing problems. The field of nanotechnology creates materials at the nanoscale, such as metallic, lipid, and natural or synthetic/semisynthetic polymers. By serving as stability enhancers, nanoparticles (NPS) can be employed in targeted drug delivery to improve the bioavailability, biodistribution and accumulation of treatments, preferably in the targeted disease area. By delivering medications to specific areas, these colloidal systems can decrease toxicity, minimize side effects, and enhance therapeutic efficacy while shielding the drug from biological deterioration and allowing for temporal and spatial management of therapies in the precise site of an illness[16-18]. In order to improve efficiency over conventional free-drug formulations, passive targeting was the basis for the initial application of nanocarriers in drug delivery. A novel method has been presented, nevertheless, which entails active targeting by adding particular ligands to improve drug delivery to target locations via conjugation techniques or magnetic fields. Nanotechnology therefore has promise for fostering innovation in medication compositions and delivery systems. An effective and site-specific distribution of chemicals makes it easier to reach a therapeutic outcome that can combat immunological illnesses, tumor diseases, or neurodegenerative disorders. In order to uncover new therapeutic targets and approaches, this Special Issue brings together various aspects of nanotechnology research, such as review papers[19,20] mathematical models to determine the body's magnetic nanoparticle trajectories or explain the structures of metal-decorated fullerenes[21-22], the drug delivery systems of various antitumoral agents[23-26] and the biocompatibilities of stealth liposomes and hybrid nanosystems containing surfactant agents[27,28].

MEDICATION ADMINISTRATION

During the past decade, nanotechnology-based drug delivery has shown significant interest where studies have enhanced the administration and the efficacy of active molecules[29,7]. By improving the solubility, stability and minimizing the toxicity of drug molecules, researchers investigated the use of chemical and biological approaches giving high clinical benefits. However, most related research is

still in the preclinical stage and safety assessment remains a difficult task. Therefore, future research should concentrate on therapeutic nanomedicine's performance modification, molecular mechanism, and potential toxicity[30]. This led to the discovery that different types of nanocarriers have many benefits, including the ability to-

(i) Prevent fluctuations in drug concentration while maintaining a consistent dose and target, (ii) provide maximum therapeutic effects while reducing side effects and toxicity risks and (iii) shield medications from enzymatic catalysis[31]. The many nanocarriers employed in biomedical applications-discussed in the ensuing sections are shown in Figure No.2.

METALLIC NANOPARTICLES

Because of their distinct physicochemical characteristics and wide range of functional groups that enable interaction with various therapeutic molecules, metallic nanoparticles have captivated researchers in the biomedical area[32]. It is interesting to note that metals like iron (Fe), zinc (Zn), and titanium (Ti), as well as metal nanoparticles like silver (Ag) and gold (Au), have the potential to be used in drug delivery systems due to their unique size, shape and composition.

GOLD NANOPARTICLES

Because they maintain high stability in the drug release process and have strong bond mechanisms via covalent and non-covalent conjugation, gold nanoparticles (AuNPs) are the most functionalized metallic nanoparticles in drug delivery[32]. These nanoparticles are created using a variety of techniques, including the colloidal approach, and they range in size and shape from 3 to 200nm[33]. Typically, the bottom-up technique of reducing gold precursors with sodium borohydride or sodium citrate yields AuNPs for use in drug carriers[34]. Drugs, enzymes, plant extract, or other compounds functionalize the resulting AuNPs. Transferrin, tannic acid, polyethylene glycol (PEG), porphyrin, and other capping agents then improve the potential delivery and therapeutic benefits[35,36] (Figure No.3).

Pharmacological interaction on the surface of gold metallic nanoparticles (AuNPs) to functionalize the through the administration of anticancer medications, functional AuNPs have demonstrated good utility in cancer therapy. The morin medication encapsulated in AuNPs stimulated tumor death in response to tumor growth in a xenograft mice model by controlling signal crosstalk and increasing the generation of reactive oxygen species[37]. A promising nanocarrier to reduce the high toxicity of 5-fluorouracil during the treatment of breast cancer was 5-fluorouracil carried on AuNPS functionalized by casein[38]. Analyzing the effective delivery of 5-fluorouracil-based AuNPS to different tumor cells, Akinyelu and Singh (2019) found a great delivery method for the treatment of cancer. Effective methotrexate-conjugated AuNPs were created in a different study, and they showed greater cytotoxicity against human choriocarcinoma cell lines than free methotrexate[39]. Additionally, doxorubicin (Dox), which is frequently employed as a model in cancer therapy, showed toxicity against the multidrug-resistant MCF-7/ADR cancer cells when bound AuNPs capped with PEG[40]. An improved Dox carrier conjugated with AuNPslipoic acid-modified PEG was created by[41] and it demonstrated stability in delivering the Dox into the human hepatocellular liver cancer cell line's nucleus. Dox-conjugated to glutathione-stabilized AuNPs demonstrated a promising delivery mechanism for feline injection-site sarcomas as a treatment for malignant skin tumors[42]. AuNPs conjugated with Dox and capped with various biopolymers showed encouraging results in treating colon cancer cell lines (DLD-1 and HCT-116) in a recent study[43]. Furthermore, the effective conjugation of Dox and varlitinib within AuNPs-PEG was investigated by[44], revealing the suppression of pancreatic cancer cell lines (S2-013 s) with little adverse effects on normal cells. Additionally, the human breast cancer cell line MDA-MB-231 was successfully suppressed by hesperidin (Hsp) loaded with AuNPs via chemical technique, which also increased macrophage formation and decreased the production of

proinflammatory cytokines (TNF, IL-1β, and IL-6). Because of AuNPs' high surface area-to-volume ratio, bioinert nature, and low immunogenicity, they are widely used in cardiovascular disorders. When AuNPs are incorporated into coiled fiber scaffolds, the myocardium contracts and relaxes quickly and robustly[45]. In order to improve cardiomyogenic differentiation[46], created a hybrid scaffold made of AuNP-loaded bovine serum albumin (BSA)/polyvinyl alcohol (PVA) nanofibers. AuNPs demonstrated effective transport of miR155 into macrophages that improve heart function in order to treat cardiovascular illnesses in diabetic patients[47]. Furthermore, compared to free levofloxacin, the administration of the antibiotic within bromelain-capped AuNPs demonstrated great control and localization of the target location while improving the antibacterial activity[48]. Furthermore[49] reported that gentamicin was conjugated with AuNPs for the purpose of enhancing and delivering severe microbial infection. Peptide drug conjugates with AuNPs, aside from chemotherapeutic medications, exhibit favorable chemical and biological properties that enhance target efficacy[50].

SILVER NANOPARTICLES

Because of their electrical conductivity, wide range of antibacterial action and localized surface plasmon resonance effect, silver nanoparticles (AgNPs) are well-suited for drug administration[51]. According to[52], medication molecules typically interact with AgNPs through a variety of linkages, including sulphide/thiol, amine/carboxylic, and azide-alkyne bio-conjugation. Using AgNPs[53] created a conjugate cell-penetrating peptide (TAT) for the treatment of multidrug-resistant cancer; this drug delivery method demonstrated exceptional antitumor effect. The anticancer activity and drug delivery of Dox and alendronate (Ald) were enhanced by the use of AgNPs as nanocarriers in cancer therapy[54]. It's interesting to note that[55] reported that the delivery system for cancer theranostic with less harmful effects was effective when using a realistic approach to transport Dox within a nanocarrier comprised of Janus AgNPs. Using a green approach[56] created a hybrid material comprising AgNPs embedded in carboxymethylcellulose (CMC) as a nanocarrier for Dox. Strong antibacterial and anticancer properties against skin cancer were demonstrated by this nanocarrier. AgNPs containing curcumin have strong conjugation characteristics, suggesting a promising delivery method for cancer therapy. Additionally, they exhibit lower hemolytic toxicity in comparison to free curcumin[57]. AgNPs-NGR-graphene oxide (GO) biocompatibility demonstrated superior Dox transport to tumor cells with strong targeting capabilities and significant potential for cancer therapy[58]. The surfactant-free AgNPs coated with nanoGO demonstrated strong anticancer effect and acted as a potent nanocarrier in an effort to improve the delivery and biosensing of Dox[59]. According to[60], the conjugation of camptothecin via an acid-labile β propionate on AgNPs' surface enhances transport and enables tracking of the mechanism "on"/"off" of the release process in tumor cells.

TITANIUM, MAGNESIUM, IRON AND ZINC NANOPARTICLES

It is well recognized that titanium oxide nanoparticles, or TiO2NPs, have the potential to greatly improve drug delivery systems' functionality. Generally speaking, there are two methods for incorporating the drug molecule into TiO2NPs: (i) soaking the particles in an aqueous drug solution, or (ii) pipetting a volume of the drug solution onto the TiO2NP surface[61]. For instance[62] successfully coupled Dox with TiNPs through electrostatic interactions, confirming improved intracellular cytoplasmic Dox transport with superior anticancer efficaciousness against the multidrug-resistant MCF-7/ADM cells. Similar to this[63] discovered that PTX-TiO2NPs exhibit greater anticancer efficacy than free PTX after using TiO2NPs to transport the anticancer medication paclitaxel (PTX) into breast cancer cells. The drugs were erlotinib (ERL) and vorinostat (SAHA). The outcomes demonstrated that by stopping cancer cells in their G2/M phase, the hybrid nanocarrier

may upregulate the cells. Furthermore, the melanoma cancer B16F10 cell lines were treated by the chitosan/cobalt ferrite/TiO2 nanofibers coupled with Dox via an electrospinning procedure. According to[64], these nanocomposites demonstrated the highest localized cancer therapy as well as the quickest release of Dox from the nanofibers. Conjugated with curcumin, mesoporous TiO2@ zinc oxide-GO nanocarriers had note worthy anticancer activity and showed promise as drug delivery vehicles for colon cancer[65]. According to[66], a recent study showcased the ability of magnetic nanoparticles (Fe3O4NPs) functionalized with 3-aminopropyl) triethoxysilane and coated with tragacanth gum and chitosan to deliver curcumin. The best-recorded release of curcumin was 60% within 120 hours.

APPLICATIONS OF NANOTECHNOLOGY IN DRUG DELIVERY TO THE CENTRAL NERVOUS SYSTEM

Among the two most prevalent neurodegenerative illnesses are Parkinson's and Alzheimer's disorders[67]. Global statistics show that stroke is linked to neurological disruption and is the second most prevalent disease in the United States after Alzheimer's[68-71]. It is also the third largest cause of mortality[72]. The research suggests that Iran has a two-fold higher stroke prevalence than either Europe or North America[73]. The World Health Organization estimates that 20 to 60 cases of multiple sclerosis occur for every 100,000 people in Iran[74,75]. Drug diffusion over the blood-brain barrier is the primary therapeutic phase for brain disorders. To achieve the best possible therapeutic outcomes against neurological illnesses, the safe, appropriate and targeted administration of medicinal molecules to the central nervous system (CNS) is an extraordinary objective[69-80].

BLOOD-BRAIN BARRIER

The brain, which is housed in a membrane known as the blood-brain barrier, is the most intricate and sensitive organ in the body. This boundary is ideal for defending brain neurons from dangerous and poisonous substances found in blood. Drug diffusion to brain tissue is also impacted[81]. Robust barriers enclose the brain, preventing the passage of any substance, including therapeutic and diagnostic agents, into the central nervous system[82]. The development of technologies for the efficient transportation of medications and molecular imaging is necessary to conceptualize the physiological features of this blood-brain barrier[83]. The bloodstream and brain are kept apart by the blood-brain barrier (BBB). The human brain has roughly 100 billion neurons. The brain's capillaries have a diameter of only 7-10μm[84]. There are extremely few entrance points from the environment into the brain due to the absence of the valvar and intracellular holes in the BBB[81-86]. Nevertheless, the BBB can be crossed and medication transport to the central nervous system (CNS) facilitated when nanoparticles (NPs) and polymer coatings are paired[87-89]. Numerous advancements in the detection and management of brain tumors, trauma and nervous system problems have been made possible by this technique[90-93]. Many therapeutic polymers are being researched for clinical usage in the treatment of cancer and other illnesses[94]. The development of novel NPs-based methods and tactics aimed at medication delivery to the brain is shown in Table No.1 and Figure No.1.

SUBSTANCE TRANSPORT ACROSS THE BLOOD-BRAIN BARRIER

Because the blood-brain barrier (BBB) restricts access to the brain and shields it from pathogens and other dangerous chemicals, pharmaceutical molecules may not be able to reach the brain while in circulation. Even tiny chemicals cannot permeate the barrier and enter the brain. Despite the fact that many necessary molecules can permeate through this barrier, medicinal chemicals are frequently left out due to their unique characteristics[96,97]. The inability of medications to pass through the blood-brain barrier emphasizes the necessity of creating NPs-based drug delivery techniques. Only a restricted range of chemicals can diffuse due to the BBB. These nanoparticles get beyond this barrier

and take several paths to neurons. The BBB has been crossed with a number of NPs[71,98,99]. The medicine is able to cross the blood-brain barrier (BBB) thanks to the NPs' ability to pierce through the tight connections between the endothelial cells in the arteries. Drug transfer across the endothelial cell layer can also be facilitated by NPs' endocytosis and transcytosis[99,100]. Lipid nanoparticles possess lipophilic characteristics that allow them to penetrate the blood-brain barrier and enter the brain via many transport channels, such as transcellular, paracellular and receptor-mediated endocytosis[97,100,101]. Furthermore, NPs have the ability to conjugate or coat particular ligands to target particular cells and through the use of these ligands, they can move from the circulation across the BBB via receptor-mediated transcytosis[102-104] NPs can cross this barrier and arrive at neurons through many pathways, as shown in Figure No.4[105].

Numerous receptors that may selectively bind to ligands and internalize into cells are expressed on the blood-brain barrier (BBB). NPs may mediate the transport of these ligands across the blood-brain barrier. The best method for delivering NPs to the brain over the BBB has been receptor-mediated transport because of the interaction between receptors and ligands[97,106,107].

Table No.1: Methods and plans for administering medications to the central nervous system

S.No	Techniques for drug delivery to the central nervous system by systemic route	Approaches	Strategy	References
1	Non-invasive techniques	Chemical	Lipophilic analogs Prodrugs Chemical drug delivery system Molecular packaging	108
2		Biological	Receptor/vector-mediated delivery of chimeric peptides Viral vectors Cell-penetrating peptide-mediated drug delivery	109
3		Colloidal drug carriers	Micelles and microemulsions Nanospheres and nanocapsules Liposomes SLNs Dendrimers Polyethyleneimine derivatives Carbon nanotubes, single- multi-walled carbon nanotubes	106
4	Invasive techniques	Pharmacological	Intracerebral implants	110

			Intraventricular/intrathecal/ interstitial delivery Biological tissue delivery	
5		Blood-brain barrier disruption	Convection-enhanced delivery Osmotic blood-brain barrier disruption strategy Biochemical blood-brain barrier disruption strategy Ultrasound-mediated blood-brain barrier disruption strategy	111
6		Alternative routes for central nervous system drug delivery	Olfactory and trigeminal pathways to the central nervous system, intranasal delivery Iontophoretic delivery	112

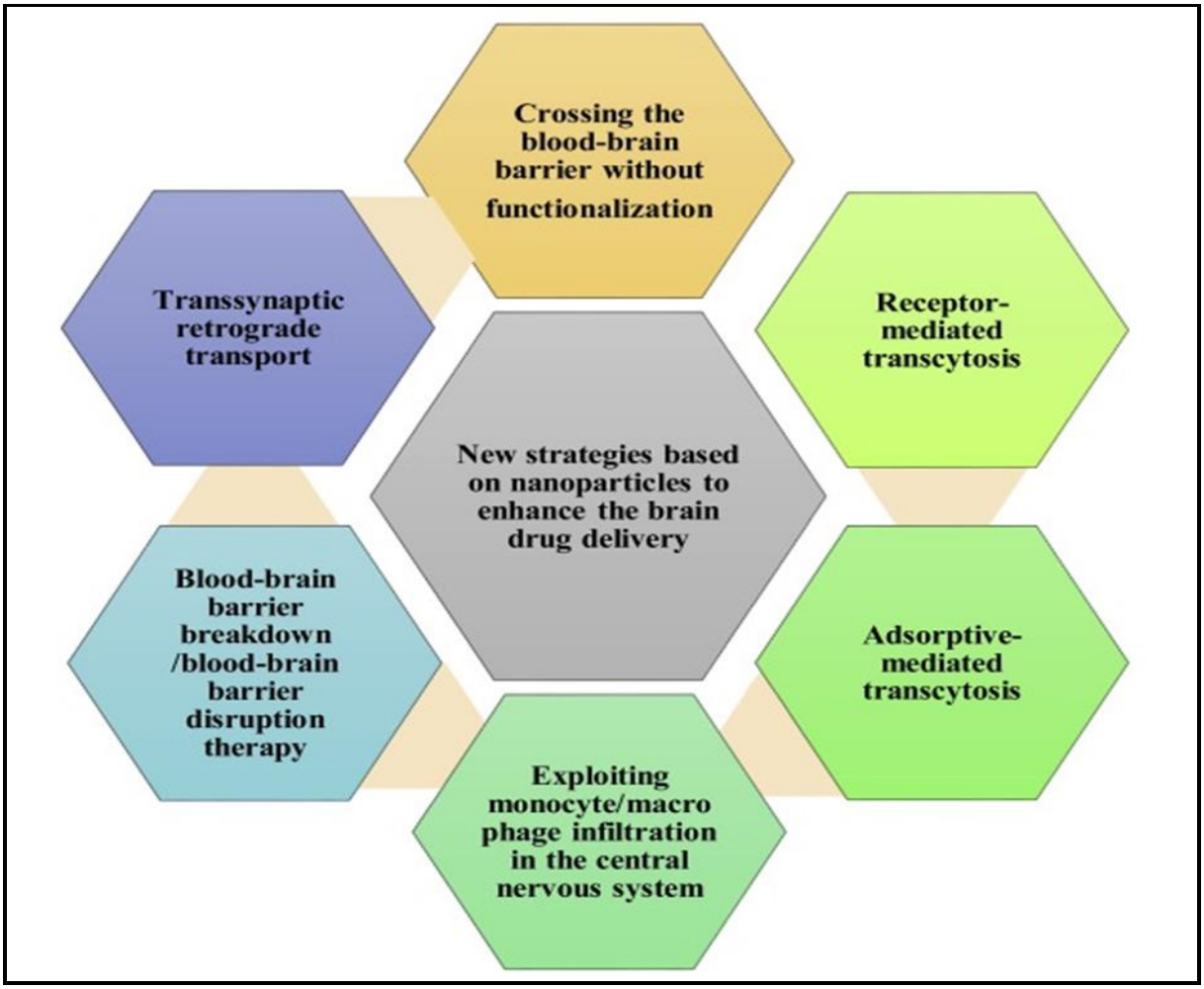

Figure No.1: Creation of novel drug delivery techniques based on NPs technology for the brain[95]

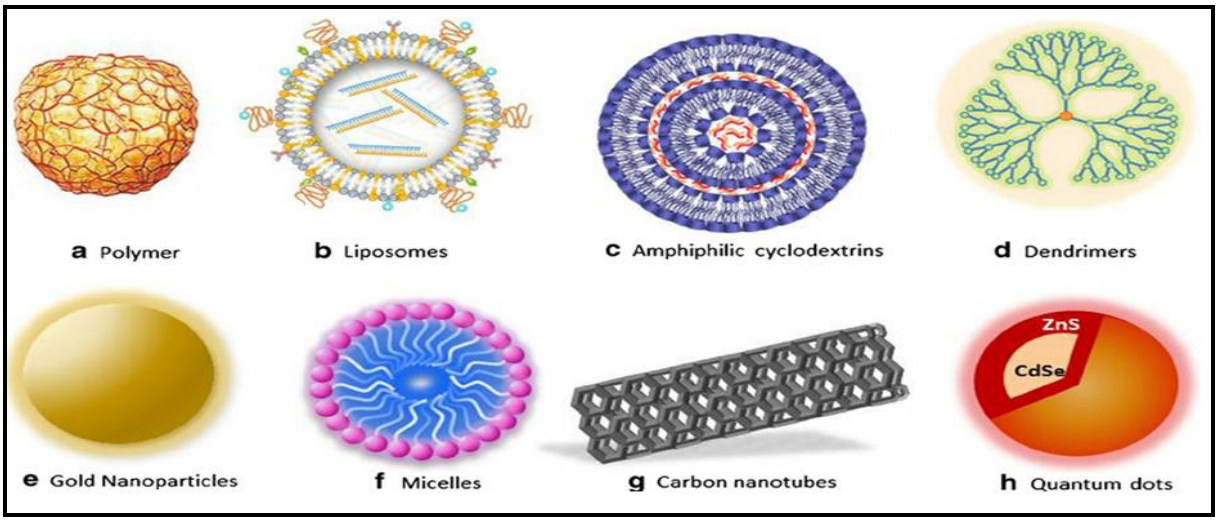

Figure No.2: Various nanocarriers are employed in drug delivery systems

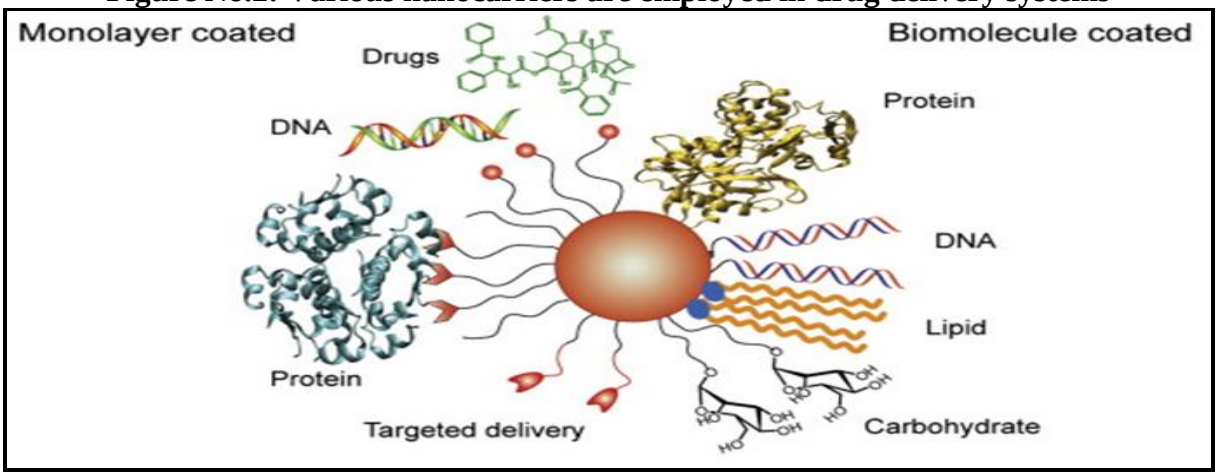

Figure No.3: Multiple drug molecule incorporations with nanocarriers

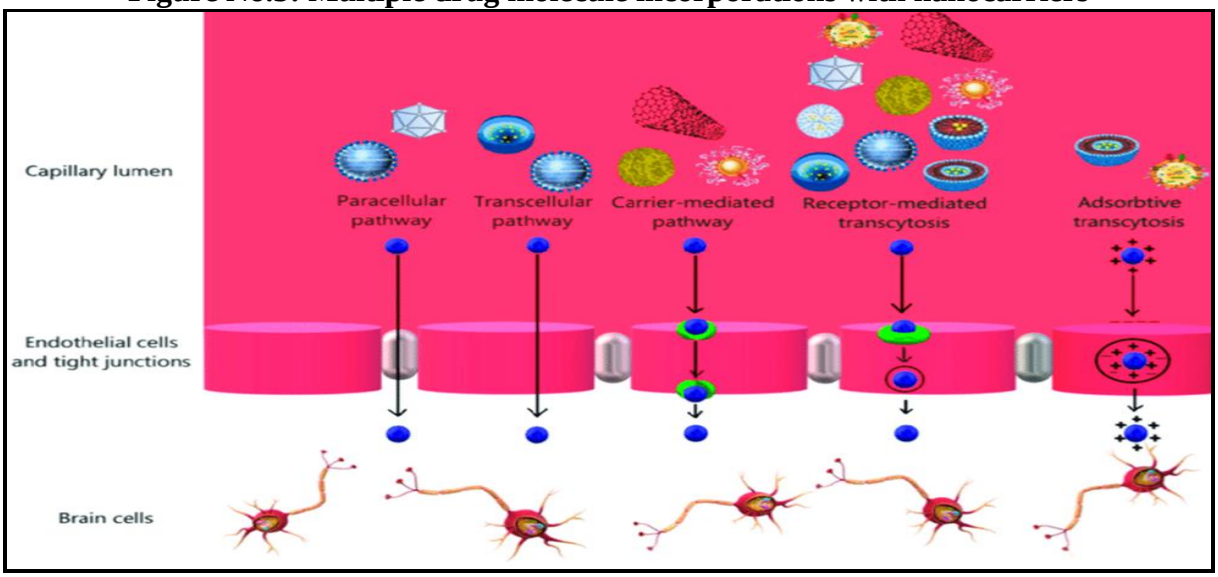

Figure No.4: Principal routes via which nanosystems can pass the blood-brain barrier

CONCLUSION

Nanomedicine, which uses nanotechnology to improve drugs and healthcare, is a new subject with great potential for the twenty-first century. Through disease localization, nanomedicine can target biological cells with medications, diagnostics, and therapeutics. Cell theory served as the basis for the diagnosis at first, but more recent research has taken us to the atomic and molecular levels. Consequently, materials with nanoscale sizes have vast surface areas, structure, and form that improve their potential for diagnosis and therapy. Nanomaterials in delivery applications so primarily aim to deliver the required molecules to their target locations while minimizing side effects and optimizing therapeutic effects.

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CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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