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Recent Trends in Treatment of Cancer using Biomaterials

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1. Introduction

A biomaterial is a substance that has been engineered to interact with biological systems for medical purposes, either diagnostics or therapeutic ones. The Clemson University advisory board for biomaterials has formally defined biomaterials as "a systemically and pharmacologically inert substance designed for implantation within or incorporation with living systems." Biomaterial science or biomaterial engineering is around fifty years old and has been experiencing steady growth since then.

Biomaterials can be driven from nature or synthesized in laboratories by using different materials such as polymers, ceramics, or composite materials. They are used in the medical field to replace an organ or a part of it, or biomedical devices which help in the functioning of the organ in the body.

The goal of using biomaterials is to improve human health by restoring the function of natural living tissue and organs of the body.

The development of biomaterials is a collaborative effort of engineers, biologists, chemists, physicists, and clinicians. They have been designing materials that can overcome the biological barriers that limit drug delivery. Biomaterials have improved the efficacy of the delivery of the drug and the range of pharmaceutical compounds including antibiotics, peptides, vaccines, among others.

Drug Delivery Mechanism

Drug delivery refers to approaches, formulations, manufacturing techniques, storage systems, and technologies involved in transporting a pharmaceutical compound to its target site to achieve a desired therapeutic effect. Principles related to drug preparation, route of administration, site – specific targeting, metabolism, and toxicity are used to optimize efficacy and safety, and to improve patient convenience and compliance. Pharmacotherapy can be defined as the treatment and prevention of illness and disease through drugs of chemical or biological origin. It ranks among the most important methods of medical treatment, together with surgery, physical treatment, radiation, and psychotherapy. Usually, the concentration of the drug in the body is determined by the plasma. this is done because the plasma is easy to access and is dependable. The concentration is measured using high - performance liquid chromatography (HPLC).

Dosages can be differentiated with their physical forms. Sometimes the phases of dosage are of the same phase as an emulsion of two liquids (oil and water) even though their phases are similar the physical properties are different such as their electrical conductivity, their thermal conductivity, density, etc. However, most of the dosages are a combination of distinct phases such as a suspension of solid in liquid therefore they are classified by their energy.

Another way of differentiating the different dosage forms is according to their site of action. A drug can be infused into the body through ingestion or infusion. The various routed of admiration a drug can be classified into:

- Direct entry into the body
- Entry into the body by overcoming the skin
- Entry into the body by overcoming the mucosal membranes

The most convenient method is the oral method however the drugs delivered through this method can be metabolized by hepatic first - pass effect (the drug gets metabolized in a specific part of the body (liver) that results in the reduced concentration of the active drug upon reaching the site.)

There are many mucosal membranes the most important mucosal membrane is the gastrointestinal tract that allows oral drug delivery. The suitability and convenience of this route of delivery make oral dosage forms the most common of all drug delivery systems. Also, the buccal, sublingual, rectal, and vaginal mucosa and indeed the lung and nasal mucosal membranes can function as absorption sites. For all these mucosal membranes dosage forms have been developed, such as buccal and sublingual tablets, suppositories, vaginal rings, inhalers, and nasal sprays, to name a few. Another way of differentiating according to their mechanism of drug release. Dosage forms can control the rate of release of a drug and/or the location of the release. They can be classified into:

- Immediate - release dosage form - Drug is released immediately after administration
- Modified release dosage form - Drug release only occurs sometime after the administration or for a prolonged period or to a specific target in the body.
- The modified - release systems are further divided into delayed - release, extended - release, and targeted release.
- Delayed release - release: drug is released only at some point after the initial administration.
- Extended - release - the drug is released only at some point after the initial administration.
- Targeted - release - release prolongs the release to reduce dosing frequency. Extended - release is classified into sustained - release and controlled – release systems.

- Modified drug release can be used to improve the stability, safety, efficiency, and therapeutic profile of the drug.

Drug Metabolism

Drug metabolism is used to describe the biotransformation of a drug in the body so that it is easier for the drug to act. Most of the metabolic process occurs in the liver. As the enzymes that help in the process are concentrated in the liver. A drug is metabolized through the following processes Oxidation, Reduction, Hydrolysis Hydration, Conjugation, Condensation, Isomerization. In most cases, the metabolized drug is inactive, however. metabolizes of some drug is pharmaceutically active and influences the body. The drug metabolism of the drug varies from person to person. some of the factors that contribute to the rate of metabolism of the drug are a genetic predisposition, chronic liver disorders, advanced heart failure, interactions with other concurrent medications.

Biomaterials and Drug Delivery Systems

The search for controlled targeted drug release without the side effects during and after the release of the drug has led to the use of biomaterial that can transport the drug in a controlled and targeted manner. usually, the medication is prescribed in a time with a measurement that will result in the recovery of the patient. In case if the concentration of the drug increases in the body, then the therapeutic effect of the drug is lost and becomes toxic to the body with can result in the dead of the patient. it is also possible that after the metabolism of the drug loses its therapeutic effect and is less effective, which is also known as drug wastage.

Nanotechnology for Drug Delivery

Nano particles refer to organic and inorganic particles that have unique properties that are selectively designed for a specific application. Nanoparticles drug delivery is a technology that uses nano particles to deliver the drug in a controlled and targeted manner. This minimizes the side effects, dosage, and dosage frequency.

Nanoparticles are small - sized particles that range between 1 to 100 nanometres in size. They are made by a solid or a liquid material that includes metals, dielectrics, and even semiconductors. they may be internally heterogeneous or homogenous. nanoparticles used in drug delivery systems are Chitosan, Alginate, Xanthan gum, Cellulose, etc.

Nanoparticles for the Treatment of Cancer

Cancer is a disease caused by an uncontrolled division of abnormal cells in a part of the body. Our human body is made up of a trillion cells. these cells grow and divide and multiply to form new cells this is called cell division. When there is an error in the cell division which can be triggered by many reasons genetics and behavioural triggers.

Cancer is a genetic disease - that is it is caused by errors in the genes that control the cell division. Usually, cancer treatment is limited to surgery, radiation, and chemotherapy. all these methods damage the tissue or incomplete eradication of the cancer cells. With the use of nanotechnology, we can target the chemotherapies to the selective cancer cells, neoplasm guides in surgical resection of tumours, and enhance the therapeutic efficacy of radiation - based and other current treatment modalities. This increases the survival rate of the patent and decreases the risk of damage.

Nanotechnology in Cancer

Nanotechnology diagnoses and treats cancer at a very tiny level, it uses the particles 100 to 10, 000 times smaller than the human cell to detect the cancer cells and to kill them. Normally doctors use imaging tests like CT scans and X - rays and MRI - scan to diagnose cancer. But these are only effects only if the cancer tissue is big enough to see, by then cancer may have spread to other parts of the body.

Due to the small size, nanoparticles can detect the changes in a small cell. It can differentiate between healthy and cancerous cells. Nanotechnology can make tumors easier to see on imaging tests. Coating nanoparticles with antibodies or other substances helps them find and stick to the cancer cells. Particles can also be coated with substances that send out a signal when they find cancer. For example, nanoparticles made from iron oxide bind to cancer cells and send off a strong signal that lights up the cancer cells on MRI scans.

Chemotherapy drug cisplatin is an effective cell killer. However, this cisplatin has side effects such as kidney and brain damage. With the help of nanoparticles, they carry the drug molecules to the targeted site.

Nanotechnology for GBM

Glioblastoma multiforme (GBM), is the most difficult type of brain tumour to treat. it is also known as grade IV astrocytoma, which is a fast - growingtumour that invades every tissue of the brain but not the distant organs. This is a devastating type of cancer that can lead to the death of a person in 6 months. It ranges from 0.59 to 5 per 100, 000 persons. And glioblastoma tumours are especially hard to treat because they are not found in a defined mass with clear borders. Instead, the tumour includes thread - like tendrils that extend into nearby areas of the brain

Researchers at MIT have devised a new drug - delivering nanoparticle for the treatment of GBM. That could offer a better way to treat GBM. These particles carry two different drugs that are designed to easily pass the brain - blood barrier (a semipermeable membrane separating the blood from the cerebrospinal fluid, and constituting a barrier to the passage of cells, particles, and large molecules) and bind directly to the tumour cells. one drug damages the tumour cells' DNA while the other interferes with the systems cells normally use to repair such damage.

"What is unique here is we are not only able to use this mechanism to get across the blood - brain barrier and target tumours very effectively, but we are also using it to deliver this unique drug combination, " says Paula Hammond, a

David H. Koch Professor in Engineering, the head of MIT's Department of Chemical Engineering, and a member of MIT's Koch Institute for Integrative Cancer Research.

The nanoparticles used in this study are based on particles originally designed by Hammond and former MIT graduate student Stephen Morton. These spherical droplets, known as liposomes, can carry one drug in their core and the other in their fatty outer shell.

The researchers found that if they coated the liposomes with a protein called transferrin, the particles could pass through the blood - brain barrier with little difficulty. Furthermore, transferrin also binds to proteins found on the surface of tumour cells, allowing the particles to accumulate directly at the tumour site while avoiding healthy brain cells.

This Targeted drug delivery allows large doses of chemotherapy drug that has unwanted side effects if injected through the body, Temozolomide, which is usually the first chemotherapy drug given to glioblastoma patients, can cause bruising, nausea, and weakness, among other side effects.

Building on prior work from Floyd and Yaffe on the DNA - damage response of tumours, the researchers packaged temozolomide into the inner core of the liposomes, and in the outer shell, they embedded an experimental drug called a bromodomain inhibitor. Bromodomain inhibitors are believed to interfere with cells' ability to repair DNA damage. By combining these two drugs, the researchers created a one - two punch that first disrupts tumour cells' DNA repair mechanisms, then launches an attack on the cells' DNA while their defences are down.

Brain metastases

Brain metastases are the most frequently occurring neurologic complications of cancer in adults, with 9–17% of all cancers resulting in brain metastasis. Primary brain tumors, on the other hand, are relatively rare and comprise about 1.4% of cancers. Treatment modalities employed for brain metastases include surgical resection, whole - brain radiation therapy, radiosurgery, and chemotherapy. The choice of treatment would usually be based on several considerations.

Glioblastoma multiforme a metastatic primary brain tumor, accounts for 12–15% of all brain tumors and is the most common primary brain tumor in adults. A major contribution to the poor survival rates is the insufficient transport of therapeutic molecules across the blood - brain barrier (BBB).

The blood - brain barrier

The treatment of brain tumors is particularly challenging, mainly because of their intracranial location. Intracranial tumors are effectively 'shielded' from the effects of most systemically administered cytotoxic agents. The brain parenchyma and most (but not all)–intracranial tumors are protected by the intact BBB, which maintains the brain microenvironment by serving as a physical and metabolic barrier regulating the access of molecules to the brain. The physical barrier is formed by the tight junctions between the adjacent endothelial cells (which prevent blood - borne substances from crossing into the brain parenchyma), a lack of capillary fenestrations, very low pinocytotic activity, and the metabolic barrier is formed by degradative enzymes, specialized transport receptors, and endothelial cell efflux pumps.

Passive targeting with nanoparticles

Nanoparticles have been used to passively target drugs to intracranial tumors, on intravenous injection, to enable the delivery of therapeutics across the BBB to the brain, as there is evidence that nanoparticles can preferentially accumulate drugs at tumor sites when compared with the administration of drugs in solution. Generally, nanoparticles may be engineered to: enable tissue or organ - specific transport of their drug payload; or enable the delivery of hydrophobic and metabolically labile drugs. Thus, nanoparticles are an interesting platform to consider in drug development for brain tumor indications.

Intravenously administered nanoparticles for delivery of therapeutic agents to brain tumors may theoretically exploit the enhanced permeability and retention effect. The formulation was also found to be less cardiotoxic. This provides indirect evidence that nanoparticles can take advantage of a variation in the BBB at the tumor site.

Nanomedicines may also consist of more than one therapeutic for the treatment of brain tumors. On intravenous injection, this nanoparticle formulation yielded superior survival outcomes in F98 glioma - bearing rats compared with the administration of the two drugs separately in solution or to the nanoparticle – containing carmustine alone.

Nanoparticles may also work by simply increasing plasma exposure, which in turn increases brain exposure while minimizing exposure to areas of potential toxicity. The nanoparticles resulted in increased plasma and brain exposure, reduced liver and bone exposure and ultimately increased tumoricidal activity (survival and tumor size) in an intracranial tumor model, without increasing myelosuppression.

Active targeting with nanoparticles

Active targeting involves the use of carriers bearing various surface ligands to achieve either transport across an intact BBB or cell uptake following extravasation across a leaky BBB. Various across BBB transporters such as TfR and GLUT have been exploited for the transport of drugs across an intact BBB.

While there is good preclinical evidence showing the efficacy of nanoparticles in rodent models of intracranial tumors, clinical evidence on the use of nanoparticles is harder to locate. There are some reports of clinical trials in brain tumor patients with passively targeted nanoparticles. However, the efficacy of this nanoparticle approach in the clinic has not yet been reported.

Table: Clinical studies on intravenously injected nanoparticles in brain cancer.

Nanoparticle type	Drug	Indication	Study Phase
Cationic liposomes	Liposomesencapsulated*p53* cDNA in combination with oral temozolomide	Recurrent glioblastoma	Phase II
Polymer - gadolinium chelates	AGuIX (polysiloxane gadolinium - chelates - based nanoparticles) concurrently with whole - brain radiation	Brain metastases	Phase I
Silica	124I - cRGDY - PEG - dots for PET scan	Newly diagnosed or recurrent metastatic melanoma, malignant brain tumors	Microdosing study
Gold	NU - 0129	Gliosarcoma, recurrent glioblastoma	Early Phase I
Liposome	CPT - 11	Recurrent high - grade gliomas	Phase I

Theranostics

Imaging agents and drugs transported by a single nanoparticle are another area of innovation that has been applied to the treatment of experimental brain tumours and these are known as theranostics. Intravenously administered polymeric nanoparticles loaded with smaller iron oxide nanoparticles (for MRI). These image - competent nanotherapeutics may prove interesting in the treatment of diffuse brain metastasis in multiple brain regions.

2. Conclusion

Glioblastoma and brain metastasis are still areas of unmet medical need and several nanoparticle formulations are showing promise in glioblastoma rodent models of the disease with a few even transitioning to clinical testing.

It remains to be seen if the promising rodent data are indeed translated to approved clinical therapies and attention will need to be turned to the issue of manufacturability if the ligand - targeting systems are to transition into clinical products.

The growth and invention of biomaterials have led to several success stories which allowed individuals to lead a long and healthy life. Modern discoveries in biomaterials and medical devices will rely on continual progress in molecular biology, polymer science, mechanical engineering, chemical engineering, and clinical practice.