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MESOPOROUS SILICA NANOPARTICLES AS TARGETED DRUG DELIVERY SYSTEM FOR CANCER

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Abstract : Mesoporous nanoparticles have emerged as a promising vehicle for targeted drug delivery in cancer therapy, offering a combination of high surface area, tunable pore sizes, and biocompatibility. These nanostructured materials facilitate the encapsulation and controlled release of therapeutic agents, enhancing drug solubility, stability, and bioavailability. Leveraging surface functionalization, mesoporous nanoparticles can be engineered to recognize and bind to specific cancer cell receptors, ensuring precise delivery of anticancer drugs while minimizing systemic toxicity. This abstract explores the synthesis, functionalization, and therapeutic efficacy of mesoporous nanoparticles in cancer treatment, highlighting their potential to revolutionize current oncological practices by improving the specificity and efficiency of drug delivery systems.

Keywords:- Mesoporous, nanoparticles, anticancer, drug delivery systems

1. Introduction

Molecular and cellular analyses have demonstrated unregulated growth, maturation, and cell survival as basic characteristics of many types of cancers. Cancer, an abnormal growth of cells anywhere in the body, is often described as a group of more than 100 different diseases that have similar characteristics. Cancer occurs when healthy cells begin to change and grow uncontrollably, forming a mass called a tumor. One of the deadliest illnesses, cancer is becoming place commonplace in the world. One-off, a big difficulty with current cancer treatments is that most therapeutic medications damage healthy tissues and organs at the same time, which has a major negative impact on normal tissues. This is because most drugs lack selectivity. The failure of many effective anticancer medicines, which are greatly impacted by the rise in multidrug resistance (MDR), is another issue.[1] Cancer continues to be one of the leading causes of death, having a detrimental effect on lifestyle choices, medical expenses, and the system of health care. Furthermore, certain cancers have exorbitant expenses or no effective curative treatments. [2]
A sequence of mutation stages known as cancer causes cells to become self-sufficient in growth signals and resistant to apoptotic and anti-proliferative pathways that would usually stop them from proliferating. This allows the cells to divide and proliferate unchecked. Exposure to carcinogens, such as UV radiation, chemicals, smoking, genetic mutations, or epigenetic changes, is one of the external stimuli that starts carcinogenic cascades. [3]
The most commonly recommended current therapy treatment method is surgically removing the tumors, sometimes in conjunction with radiation therapy or chemotherapy medications. Surgery is one of these treatments that works best while the cancer is still in its early stages. Most chemotherapeutic medications still cause the death of healthy tissue, even though mortality and morbidity have decreased with chemotherapy. Drug resistance, which develops when cancer cells that were initially repressed by an anti-cancer therapy start to become resistant to the agent, is a major challenge with chemotherapy. The main causes are an increase in drug efflux and a decrease in medication absorption. Traditional non-targeted chemotherapy has several drawbacks, such as difficult dose administration, poor selectivity, rapid drug metabolism, and serious adverse effects. [4]

In this regard, systems that target and deliver chemotherapeutic drugs to tumor locations are increasingly being developed using nanotechnology as a key component. These nanocarriers can carry chemotherapeutic medicines, genetic material, imaging agents, biomarkers, or mixtures of these things, in response to physical and biological stimuli [4]. Several factors, including circulation, bio-distribution, tumor accumulation and penetration, cellular uptake, and subcellular distribution greatly impact the efficiency of tumor-targeted drug delivery. One of the most important characteristics of nanoparticles is size. Drugs incorporated in nanoparticles inside solid tumors are never able to disperse uniformly due to deep penetration, which is always impeded by the high fluid pressure

and tight matrix present within the tumor. This relates to the previously discussed link between intra-tumor behaviors and nanoparticle size. [5]
Mesoporous nanoparticles (MSNs), one of the type of nanoparticle drug carriers, have drawn a lot of interest due to their special inherent qualities, which include their large specific surface area, tunable shape, particle size, surface charges, pore size and volume, and nontoxic nature. [6]

2. Types of cancers

Cancers are broadly classified into 2 types according to the type of cell from which they arise:

1) Benign tumors

Benign tumors are not "cancer" and do not spread widely throughout the body, although they can grow substantially and damage surrounding tissues, if not treated.

2) Malignant tumor

A malignant tumor is a collection of cells that are uncontrollably growing (dividing beyond normal boundaries), invading (entering and destroying surrounding tissues), and occasionally metastasizing (spreading to other parts of the body through lymph or blood). These three characteristics set malignancies apart from benign tumors. The only known mechanisms for metastasis are infections and malignant tumor cells. [7]

3. Conventional treatments

3.1 Chemotherapy

Chemotherapy mainly functions by preventing the cancer cells from proliferating and dividing. In addition to growing and dividing far more quickly than normal cells, Cancer cells have high levels of endogenous stress and divide and grow faster than normal cells. Consequently, in contrast to other nearby cells, the medications can kill them faster and more thoroughly. angiogenesis inhibitors, histone deacetylase (HDAC) inhibitors, mechanistic target of rapamycin (mTOR) inhibitors, poly (adenosine diphosphate-ribose) polymerase (PARP) inhibitors, tyrosine kinase inhibitors, and proteasome inhibitors are a few of the promising inhibitor therapies that have been used to treat solid cancers. Varied forms of chemotherapy may have varied effects on the target cells. Certain treatments have the potential to directly modify the quality of cellular proteins, resulting in their non- functionality and impacting critical physiological pathways within cells. These groups of compounds include major chaperone repressors, autophagy suppressors, and proteasome inhibitors. [8]
Chemotherapy medications can be delivered subcutaneously (SC), intrathecally (IT), intravenously (IV), or orally. The majority of chemotherapy drugs are delivered intravenously due to their 100% absorption rate. Certain chemicals, like paclitaxel, require mixing with solvents like cremophor to improve absorption because they are poorly soluble. The liver and kidneys are responsible for the metabolism and excretion of several chemotherapeutic drugs. Certain chemotherapy medications can damage the kidneys or liver. In these situations, toxic levels may accumulate and result in organ failure. [9]
The side effects and long-term sequelae of anti-cancer chemotherapy remain a major source of concern for both patients and clinicians. Nausea and vomiting are amongst the most feared side effects for patients embarking on cancer chemotherapy. gastrointestinal side effects of cancer chemotherapy are also common and can be both distressing and potentially fatal for patients. Central and peripheral neurotoxicity caused by anti-cancer drugs can last many years after the end of treatment and can dramatically reduce functional capacity and quality of life in cancer survivors. Chemotherapy-induced peripheral neuropathy (CIPN) is caused by many anti-cancer drugs including platinum-based agents, vinca alkaloids, taxanes, and proteasome and angiogenesis inhibitors. Long-term CIPN is associated with high morbidity including depression, ataxia, and insomnia. [10]

3.2. Radiotherapy

Radiotherapy [RT] is a high-energy ionizing radiation-based therapy, is effective for the treatment of most human malignancies. At some time during their cancer treatment, almost half of all patients will receive radiotherapy, which is one of the most affordable treatments for cancer treatment. Radiation therapy can be applied as a monotherapy or in a multidisciplinary setting in conjunction with other forms of treatment. [10] RT is also known as X-ray therapy or irradiation. Radiation causes the cancer cell's DNA to become punctured, which stops the cells from growing and dividing and ultimately leads to their destruction. [11] It is possible to deliver radiation internally or externally. In the first modality, an external radiation source delivers the radiation beam; in the second, a radioactive source is inserted inside the lesions that need to be treated. [12] Radiotherapy has many side effects mainly Distress, Anxiety, Depression, and Fatigue. [13]

4. Challenges of targeted cancer therapy

Because of the restricted distribution of cell surface receptors and internal targets on nonneoplastic host cells, targeted anticancer therapies were thought to be less harmful than conventional chemotherapy when they were introduced. The targeted drugs indeed reduce the side effects of chemotherapy that are typically associated with it, like nausea, vomiting, and neutropenia. Unfortunately, in addition of several toxicities that are similar to those of standard chemotherapy but may have different mechanisms, such as diarrhea and mouth ulceration, they also have a whole new set of toxicities that were initially unexpected, including rash, cardiac dysfunction, thyroid dysfunction, hypertension, and bleeding. This is true for all toxicities, including oral toxicity, where new mechanisms of toxicity necessitate new therapies. [14]
Another major issue facing medication delivery systems generally is the toxicity of the particles utilized in distribution; certain nanomaterials can be hazardous to both human health and the environment. Experiments conducted both in vivo and in vitro have

demonstrated the deleterious effects of using silver, gold, silica, and titanium as drug- delivering and coupling nanoparticles. The applications of carbon nanotubes in medication delivery, gene therapy, and bioimaging have grown significantly. because studies have shown that carbon nanotubes can damage genes, the liver, heart, neurons, the immune system, and embryos. Researchers are particularly concerned about the use of carbon nanotubes in drug delivery because of their capacity to cross cell membranes even when they are used as carriers for biomolecules. Although carbon nanotubes have shown favorable results in their use, it is important to carry out crucial toxicity tests to ensure their safety before a widespread application in treatment. [15]

5. Nanomaterials for targeted drug delivery

Cancer diagnosis and treatment are being revolutionized by the quickly emerging field of nanomedicine. Because of their small size (diameter between 1 and 100 nm) and great surface area to volume ratio, which enable them to bind, absorb, and carry anticancer agents like medicines, DNA, RNA, and proteins along with imaging agents with high efficiency, nanoparticles have special biological features. Chemotherapy-related nanocarriers can be broadly categorized into two types: those with an inorganic core (often metals) and those that use organic molecules as a primary building block for targeted or non-targeted drug delivery. Liposomes, lipids, dendrimers, carbon nanotubes, emulsions, and synthetic polymers are examples of organic nanocarriers. In contrast to polymer-based nanoparticles, inorganic nanocarrier platforms have a large surface area, better drug loading capacity, better bioavailability, fewer toxic side effects, controlled drug release, and a tolerance towards most organic solvents. These advantages have led to an intense investigation of inorganic nanocarrier platforms for therapeutic and imaging treatments in recent years. carbon nanotubes, layered double hydroxides, quantum dots, Mesoporous silica, and magnetic nanoparticles are frequently employed in cancer treatment in different ways. [16]

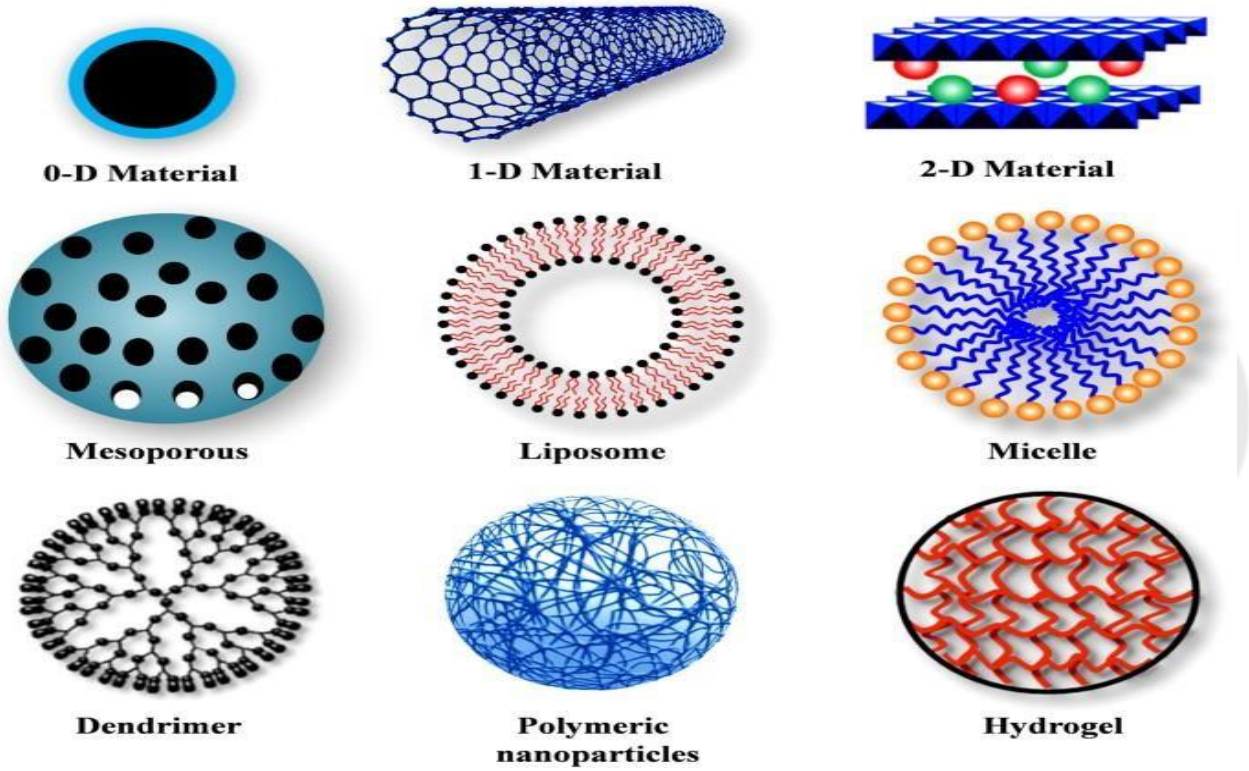

Fig 1. Different types of nanocarriers are used as targeted delivery vehicles for cancer treatment.
[16]

5.1 Mesoporous Nanoparticles

Mesoporous materials have been gradually developed since their biological properties were discovered to be used as targeted drug-delivery carriers. By using controlled synthesis, a range of new mesoporous nanoparticles have been created, offering benefits such as increased pore volume, surface modification, and improved biocompatibility. Mesoporous nanoparticles are significant for

prolonged drug release, targeted drug delivery for cancer, and blood drug concentration management because of their special drug-delivery capabilities. Mesoporous nanoparticles are transforming the way that cancer is diagnosed and treated on an individual basis by creating surface-modifying proteins and using fluorescent dye guidance to target peptide molecules. Drugs or particles administered locally to liver cancer may collect in the tumor region and achieve gradient concentrations due to the design of the majority of mesoporous nanoparticles. [17]

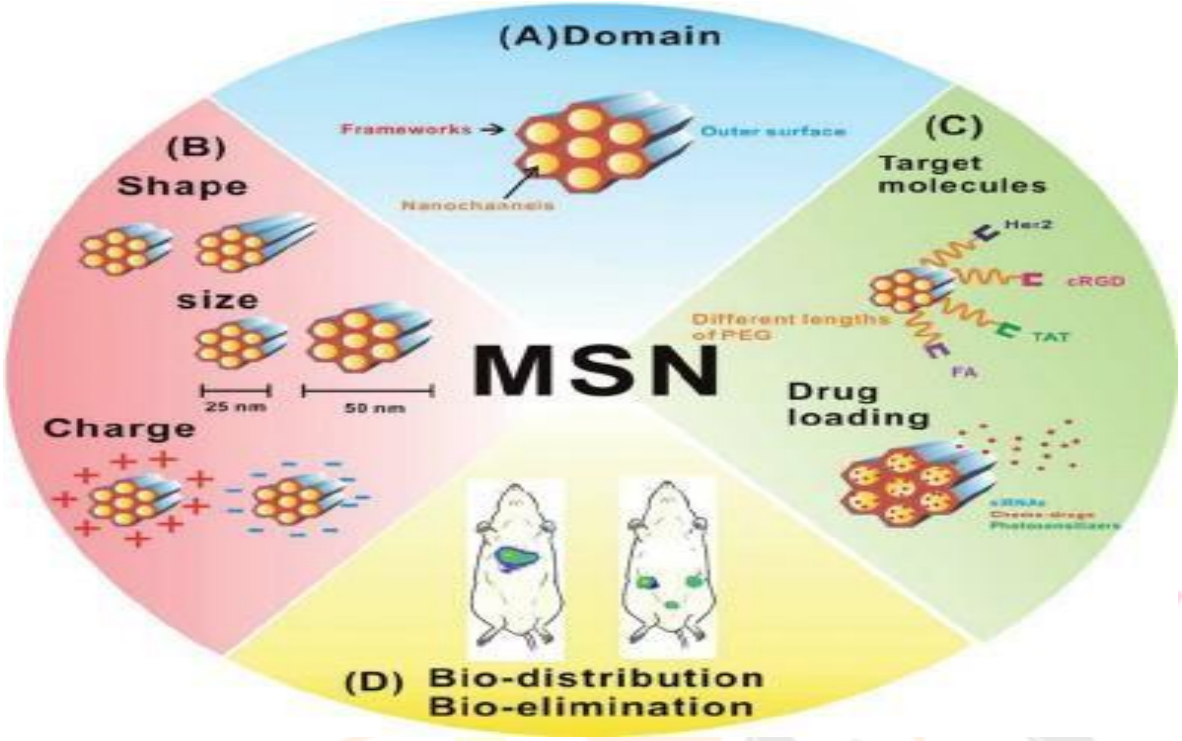

Fig 2. Mesoporous nanoparticle for targeted drug delivery system. [18]

Mesoporous silica can be functionalized with various chemical groups, enabling targeted delivery of medications and gradual release over time. [19] Mesoporous silica nanoparticles involve the identification of precise targets (cells and receptors) related to specific clinical conditions, and it is a choice of the appropriate nanocarriers to achieve the required responses at the target site while minimizing the side effects of the respective target molecule. [20]

6. EPR effect

The distinct pathophysiological feature of the solid tumor vasculature is known as the enhanced permeability and retention effect, or the EPR effect. The EPR effect has been widely acknowledged as one of the common pathophysiological features of solid tumors because of its significance for comprehending tumor vessel transportation regulation. It also serves as a basic tenet for the development of tumor-targeting drug delivery systems. [21]

This idea of EPR-based tumor-targeted therapy introduces nanomedicine—a branch of nanotechnology—into cancer chemotherapy. Numerous nanoplatforms, such as liposomes, mesoporous nanoparticles, polymeric micelles, and polymer conjugate nanoparticles, have been created as targeted drug delivery systems. A significant concern in the field of nanomedicine is what happens to nanoparticles once they accumulate in tumor tissues due to the EPR effect. Although complete nano drugs accumulate in tumors at high concentrations, their anticancer activity will be reduced if the active drug component is not released progressively into tumor tissues. A further concern that needs to be addressed is that the EPR effect is a blood vessel phenomenon, and as such, it may vary based on the clinical features and conditions of the patient or tumor. [22]

6.1 EPR effect on drug delivery

The building blocks of nanoscale drug delivery are the agent's accumulation in tumors as a result of the EPR effect and the subsequent release of their therapeutic payloads. When compared to crucial normal organs, EPR effects are not as significant, providing a delivery increase of less than two times. Through the EPR effect, the medicine is more likely to extravasate into the tumor the longer it is in circulation, but it can also extravasate into normal tissues, more slowly. Therefore, techniques that enhance the local EPR impact within the tumor, although momentarily, are required to enhance the drug's selective uptake within the tumor and, consequently, its therapeutic effect. [23]

6.2. Tumor targeting strategies

Regarding the tumor targeting strategy, two kinds of targeting strategies are there,

1) Active Targeting

It is important to remember that active targeting is necessary to transport medications, genes, and therapeutics to the desired site while avoiding normal tissues. This increases the effectiveness of treatment and reduces adverse effects. When compared to passively targeted nanosystems or free drugs, active targeting can deliver a substantially higher amount of drug to the target cell. The so-called active targeting can even boost treatment efficiency after it has accumulated in the cancer area. This is accomplished by adhering ligands to receptors that are overexpressed on cancer cells and decorating the surfaces of the nanocarriers with them. This tactic will increase the nanocarrier's affinity for the cancer cell surface, enhancing medication penetration. [24]
Active targeting, which targets specific chemicals or receptors in tumor cells such as transferrin, folate, integrin receptors, epidermal growth factor, antibodies, glycoprotein, etc., is another popular tumor-targeted technique. [25]

2) Passive Targeting

The effective passive targeting of nanoparticles requires careful consideration of various features, including surface changes, shape, and particle size. Particles must have a diameter of at least 10 nm to avoid renal clearance, and a size of 100–200 nm appears to be ideal to also avoid the mononuclear phagocytic system. Furthermore, passive targeting based on the EPR effect is also influenced by the form of the nanoparticles. Given the high blood flow rates of the liver, spleen, and lung, it is not surprising that these organs had the greatest accumulation when using short- and long-rod MSN. However, long-rod MSN was dispersed throughout the spleen with comparatively sluggish clearance, whereas short-rod MSN preferred to collect in the liver with a quick clearance rate. [26]
One factor contributing to the retention of NPs in tumor is the absence of normal lymphatic outflow. However, tiny molecule medications, which have a nearly instantaneous circulation time and rapid washout from the tumor, are not covered by this special property. Thus, the pharmacokinetics (longer systemic circulation) of small-molecule medications are improved, some tumor selectivity is provided, and side effects are reduced when these compounds are encapsulated in nanosized drug carriers. Known as "passive" cancer targeting, it does not have a ligand for particular tissue or organ binding; instead, it depends on the features of the carrier (size, circulation time), the tumor biology (vascularity, leakiness, etc.), and other factors. [24]

7. Stimuli responses of mesoporous nanoparticles

The development of a drug delivery system using smart nanoparticles that react to certain stimuli has garnered significant attention recently, owing to its immense potential for both therapeutic and diagnostic applications. For the production of stimuli-responsive MSNs, two approaches are used that are Endogenous stimuli and Exogenous stimuli.

7.1. Endogenous stimuli

Endogenous stimuli have been shown to enhance the selectivity of therapeutic action when they are specifically applied to damaged tissue. It requires adding an appropriate substance to MSNs that react to specific endogenous stimuli. With bioresponsive therapeutic efficacy, the MSNs naturally enable tumor-therapeutic selectivity and efficiency. Endogenous biological triggers include pH, redox, glucose, and enzymatic systems. [27]

7.1.1. pH-responsive

Low pH is one of these stimuli that is easiest to achieve and has been the subject of many oncology research studies because the extracellular pH of normal tissues and blood is roughly 7.4, while the pH in a tumor microenvironment is between 6.0 and 7.0, primarily due to high levels of CO2 and glycolysis rate. When a tumor's extracellular milieu gives way to intracellular organelles like lysosomes (pH<5.5) and endosomes (pH=5.5), the pH value will decrease even more. Consequently, there are chances to develop pH-responsive MSNs as regulated drug delivery systems for cancer treatment because of the aberrant pH gradients and the benefits of MSNs. [28]

7.1.2. Redox responsive

Given the high levels of reduced glutathione (GSH) in cancer cells, redox stimuli- responsiveness attracted increasing attention. Tissue extracellular fluid has a concentration of 2 μM of GSH, but the cytoplasm of normal cells has a concentration of up to 10 mM. Notably, tumor cytoplasm cells have four times more GSH than normal cells. Redox-driven capped MSNs connected by a disulfide linker will release medications as needed because disulfide bonds may be broken by GSH in cancer cells. [29] Disulfide bonds can be easily broken down by reducing glutathione into sulfhydryl groups, which causes the degradation of carriers and facilitates the release of cargo.
Redox-responsive nanocarriers have three key benefits. First, they frequently remain stable in healthy tissues, which can lessen the biological toxicity and adverse effects of the cargoes as well as the carriers. Secondly, they exhibit a fast reaction (often a few minutes to hours) to elevated GSH concentration in tumor cells to release payloads. Finally, the release in the cytoplasm is frequently anticipated to have superior therapeutic benefits in comparison to other possible sites of cargo release.
[30]

7.1.3. Glucose responsive

There has been a lot of research done on cancer starvation therapy. The Warburg effect states that although oxidative phosphorylation preferentially produces adenosine triphosphate (ATP) in normal cells with a regular microenvironment, tumor cells exhibit an enhanced, albeit less effective, process of glycolysis to produce ATP. Proliferating cancer cells tend to absorb more glucose than normal tissues to make up for this and produce more energy. Thus, it has been suggested that cancer fasting therapy involves preventing the supply of glucose or increasing the amount of nutrients that cancer cells consume.
Due to its potential to oxidize glucose into gluconic acid and H2O2, glucose oxidase (GOx) has garnered increased attention about glucose biosensors. As everyone is aware, H2O2 actively participates in several physiological functions, such as immunological response, senescence, and cell proliferation. A prior article said that endogenous quantities of H2O2 could trigger the malignant transformation of normal cells, but at high concentrations, this would result in the death of cancerous cells. Consequently, adding GOx to tumor therapy would increase endogenous H2O2 levels, which would strengthen intratumoral cytotoxicity, as well as cause intracellular glucose to be consumed, cutting off the energy supply.
Mesoporous silica nanoparticles (MSNs) possess a high degree of biocompatibility, a large pore volume, consistent pore size, high surface area, and facile surface functionalization, making them one of the most promising drug carriers. As a result, MSNs were used to deliver GOx, and the chemotherapy drug would be a desirable option. [31]

7.1.4. Enzyme responsive

Enzyme activity is vital to every biological and metabolic process in the human body. The precise chemical events that are catalyzed by certain enzymes and result in the degradation, dissociation, or morphological changes of the parent NPs are the source of drug release from NPs in an enzyme-responsive manner. Severe destruction of NPs exposed to enzymes, which typically results in burst release of pharmaceuticals, is neither required nor desirable to establish a regulated release profile of drugs. Controlled modifications to the macro-scale structure of NPs typically result in the desired controlled release of pharmaceuticals in a tumor microenvironment containing particular enzymes. [32]

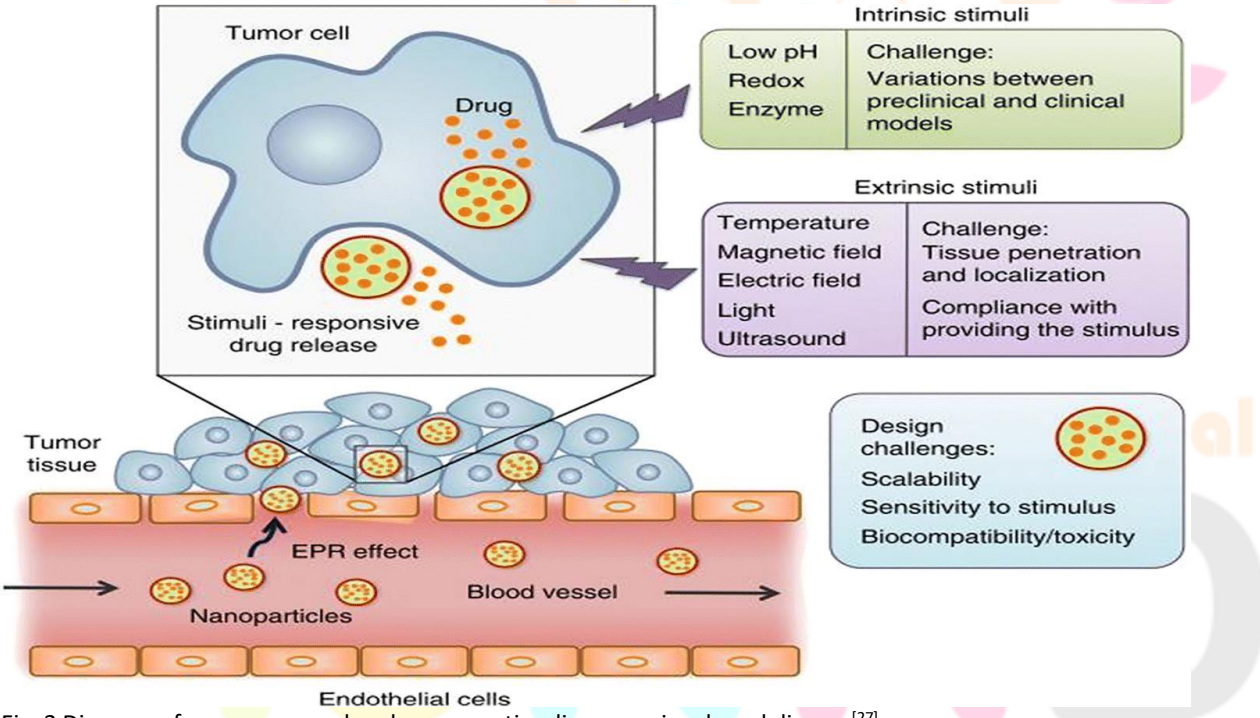

Fig. 3 Diagram of exogenous and endogenous stimuli-responsive drug delivery. [27]

7.2. Exogenous stimuli

It is possible to apply exogenous-type stimuli by utilizing external factors including temperature, magnetic, and ultrasound. The goal of endogenous or exogenous stimuli is to cause a drug's desired release at certain bodily sites. This strategy is useful for reducing a drug's adverse effects and directing its precise distribution to the intended location. [27]

7.2.1. Temperature responsive

One of the most researched stimuli-responsive drug delivery techniques has been extensively studied in the field of tumor therapy: thermo-responsive drug delivery. The materials that make up a thermo-responsive MSN drug delivery system are typically surface-coated thermo-responsive materials. The change in the ambient temperature to regulate the nanovalves switch was directly related to the release of the medication. It is commonly known that Poly N-isopropyl acrylamide (PNIPAM) is a thermoresponsive polymer. Thermo-responsive DDS was created by covalently functionalizing PNIPAM onto silica nanoparticles using a mixture of click chemistry and reversible addition-fragmentation chain transfer. The PNIPAM polymer layer on the outside of the MSN may undergo conformational changes brought on by heat, which might be utilized as a switch to regulate the release of cargo. Over 30°C causes PNIPAM to become hydrophobic, and the drug molecule and polymer chains that have accumulated on the SiO2 surface are

blocked in the MSN nanopores. The outer zone of PNIPAM brushes is still hydrophilic at 25–30°C, and the polymer chains are stretched and swelled in an aqueous solution at this temperature. The substance could be swiftly liberated from its entrapment. Temperature-sensitive MSN using a comparatively straightforward method for triggered drug release. [33]

7.2.2. Magnetic responsive

One characteristic that is employed to create magnetically sensitive nanoparticles is the type of applied magnetic field. While certain systems, in the presence of an alternating magnetic field, experience a temperature increase that leads to the destabilization of the structure and drug release, other systems have nanoparticles that are magnetically guided toward the specific tissue to carry out the drug release. The foundation of these systems consists of hybrid core–shell nanostructures made of silica and a paramagnetic or superparamagnetic component. Although the external stimulation affects the magnetic component, the silica increases biocompatibility, reduces toxicity, and offers stability.

Moreover, mesoporous nanoparticle-based magnetically responsive drug delivery systems are employed because of the many benefits of silica, such as its ease of functionalization, which enables the incorporation of diverse functional groups and permits interactions with small molecules, directing molecules therapeutic agents. MSN-based magnetically responsive nanoparticles were developed with monodispersed Fe3O4 nanoparticles as capping agents. [34]

7.2.3. Ultrasound responsive

Because ultrasound (US) is noninvasive and simple, it is a great technique for delivering targeted drug release and targeting tumors without endangering healthy tissues. The drug release and tumor penetration can be regulated by altering the exposure duration time, certain cycles, and frequency. The US can use a technique called cavitation to force the medicine out of various carriers. Low US frequencies can be used to obtain the cavitation. Cavitation increases vascular permeability to cause the inflow of prepared MSN at the cellular level while promoting the destabilization of MSN for medication release. [35]

MSN-based ultrasound-responsive system for regulated medication release. To function as a gatekeeper, the temperature-ultrasound dual responsive random copolymer p(2-(2-methoxy ethoxy)ethyl methacrylate-co-tetrahydropyranyl methacrylate), where 2-(2-methoxy ethoxy)ethyl methacrylate is a type of temperature-responsive monomer and tetrahydropyranyl methacrylate is a type of ultrasound-responsive monomer, was grafted on the MSN surface. The temperature discussion serves as a model medication loading on/off switch. While the model drug molecules could diffuse into the open nanopores at 4°C due to the hydrophilic coil-like conformation of 2-(2-methoxy ethoxy) ethyl methacrylate, at 37°C the hydrophobic polymer tightly compressed against the MSN to block the drug molecules in the nanopores. [33]

7.2.4. Photodynamic Therapy

In recent decades, photodynamic therapy (PDT) has received a lot of interest as a treatment for a variety of cancers, including esophageal, bladder, skin, and lung cancers. A cutting-edge, quickly evolving, noninvasive technique for identifying and treating cancer is photodynamic therapy. PDT uses a harmless dose of photosensitizer (PS), which can be applied locally or systemically. At first, the PS is indiscriminately dispersed throughout the body and builds up in the tissues around tumors. Depending on how the photosensitizers are administered and what kind they are, it can take anywhere from five minutes to twenty-four hours for the PS to reach its target spot. Then, the target problem is exposed to light irradiation at a particular wavelength known as the photodynamic window (600–850 nm). In the presence of endogenous molecular oxygen (O2), this produces cytotoxic reactive oxygen species (ROS), which ultimately causes cancer cells to die off or regress. [36]

It has been demonstrated that mesoporous silica has several benefits as a PS carrier. A family of porous silica nanoparticles with pore diameters ranging from 2 to 50 nm is known as mesoporous silica nanoparticles or MSNs. The main advantages of MSNs are their porosity, which results in a large surface area that is ideal for drug loading through adsorption; the controllable pore size and dimensions allow for dynamic drug release; the ease of surface modification allows for the incorporation of targeting, imaging, and other auxiliary functions; their biocompatibility; and the wealth of information surrounding their degradation and excretion. As a result, MSNs are frequently used as PS medication transporters. [37]

8. Future Prospective

The state of MSNs in clinical trials as of right now is discussed. The development of straightforward yet effective MSN-based nanoplatforms, a thorough understanding of the in vivo action mechanism, and a comprehensive toxicity investigation constitute the three primary areas of current MSN research challenges, notwithstanding many advancements.

Even though several silica-based nano-formulations have advanced to the clinical trial stage and demonstrated impressively high efficacy and acceptable safety, this is insufficient considering the enormous upfront costs incurred by the researchers. Thorough and methodical toxicity testing of MSNs is the primary factor propelling the successful clinical translation. Even though the scientific community has established a rather comprehensive collection of toxicity research on MSNs, further work is still required. Notably, a large number of the therapeutic methods for MSNs that are now under development are not linked to comprehensive toxicological assessments. While some studies have concentrated more on the therapeutic effects, the viable MSN-based nanocomposites that have been developed on this basis are very different from the silica NPs that have been employed by another group of researchers to evaluate the toxicology of MSNs. Further study focusing on the toxicological evaluation and long-term biosafety assessment of MSNs will be advantageous in promoting the prospect of their clinical translation, provided that the efficacy of MSN-based nanomedicines is guaranteed.

It is required to build straightforward yet effective MSN-based nanoplatforms. Multifunctional nanocarriers (MSNs) have been widely used because of their plentiful properties. This has led to the incorporation of two or more components
into MSNs. The intricacy of these multifunctional nanoplatforms appears to be detrimental to the preparation for scale-up and clinical translation, even though they have shown to be highly effective in several publications. On the one hand, it is commonly

known that the synthesis techniques employed at the laboratory level for MSN differ significantly from those employed in the industrial scale-up production necessary for clinical screening and application. Simplifying the production stages is the key to promoting industrial scale-up production in this method, where batch stability and repeatability of nanoformulations are always critical factors to take into account. But the sophisticated MSN-based nanoplatforms demand more advanced technologies for preparing nanoformulations and stricter storage practices, which frequently call for greater time, energy, and financial outlays. However, since we still don't fully understand the toxicity processes of MSNs, it seems to be extremely difficult to systematically uncover the toxicity mechanisms of these many components. On the other hand, the diverse components could introduce additional risk factors. Consequently, it is advised to minimize the MSNs-based platform while yet fulfilling the clinical specifications. [38]

10. Conflicts of interest

There are no conflicts of interest to declare.

11. Funding

No funding was obtained from any sources.

12. Data Availability

All supporting data has been provided in the manuscript.

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