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Advancement in Surface Functionalization of Nanoparticles: Enhancing Targeted Drug Delivery for Cancer Therapy

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ABSTRACT: Nanoparticle delivery systems have become increasingly prominent in both preclinical and clinical settings due to their versatile applications in drug delivery. Nanoparticles, typically ranging in size from 10 to 1000 nm, offer several advantages as drug carriers, including the ability to modify particle size and surface characteristics for targeted delivery, control over drug release, and site-specific targeting. Various methods, such as surface encapsulation, in situ synthesis, and self-assembly, are employed to functionalize nanoparticles, ensuring stability, biocompatibility, and functionality. Surface functionalization is particularly critical for enhancing nanoparticle performance in biomedical applications. Functionalized nanoparticles are used extensively in cancer treatment, benefiting from their ability to exploit the Enhanced Permeability and Retention (EPR) effect, which allows them to accumulate in tumour tissues. By conjugating targeting ligands, such as antibodies, nanoparticles can achieve active targeting, enhancing therapeutic efficacy while minimizing side effects. This review highlights the significance of surface functionalization techniques and their applications, particularly in targeted drug delivery and overcoming drug resistance in cancer therapy. The continued development of functionalized nanoparticles holds great potential for improving the precision and effectiveness of cancer treatments.

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INTRODUCTION:

Nanoparticle and microparticle delivery systems have been widely investigated preclinically, with many particle-based formulations and technologies already introduced in clinical settings.

Proven methods for the delivery of nanoparticles and microparticles include oral, local, topical, and systemic administration.

These methods have received approval from the Food and Drug Administration (FDA), depending on the desired application or targeted site [1].

Nanoparticles are defined as particulate dispersions or solid particles with sizes ranging from 10 to 1000 nm. The advantages of using nanoparticles are shown in Fig 1, as a drug delivery system include the following:

Fig 1. Advantages of Nanoparticles.

ADVANTAGES OF NANOPARTICLES:

Manipulability:

The particle size and surface characteristics of nanoparticles can be easily adjusted to achieve both passive and active drug targeting following parenteral administration.

Diagnosis and Treatment:

Nowadays nanoparticles can be used for early diagnosis of some diseases like neurodegenerative disease and cancer.

Controlled Release:

Nanoparticles can regulate and sustain drug release during transportation and at the site of localization. This ability alters the organ distribution of the drug and influences subsequent drug clearance, which can enhance therapeutic efficacy and reduce side effects.

Modulation of Release:

The characteristics of controlled release and particle degradation can be readily modified by selecting appropriate matrix constituents. Drug loading can be relatively high, and drugs can be incorporated into the systems without undergoing any chemical reactions, thereby preserving the drug's activity.

Site-Specific Targeting:

Achieving site-specific targeting is possible by attaching targeting ligands to the particle surfaces or utilizing magnetic guidance.

Versatile Administration:

The nanoparticles can be employed for various routes of administration, including oral, nasal, parenteral, and intra-ocular, among others [2,3].

To utilize nanoparticles for biological applications, the surface of the nanoparticles must be properly functionalized to ensure stability, biocompatibility, and functionality.

To effectively tailor and enhance the surface of nanoparticles, chemists have developed various strategies to introduce the desired functionalities. These strategies include:

Surface Encapsulation:

A method whereby specific materials are encapsulated on the nanoparticle surface to improve performance.

In Situ Synthesis:

This approach involves synthesizing functional groups directly on the nanoparticle surface during its formation.

Self-Assembly:

Utilizing molecular interactions to spontaneously organize nanoparticles into desired structures with functional properties.

These methodologies allow for appropriate customization of nanoparticles, ensuring their suitability for various biomedical applications [4].

Nowadays, Nanoparticles have been widely functionalized with a variety of materials, such as silica, synthetic polymers, biopolymers, dendrimers, and small molecules [5].

Surface functionalization of nanoparticles involves the application of covalent and noncovalent bonds—such as hydrogen bonds, electrostatic forces, and van der Waals interactions - to integrate various organic and inorganic molecules at the nanoscale. Typically, multiple linker molecules are employed to establish covalent bonds between ligands and the surfaces of nanoparticles [6].

The surface properties of nanoparticles, such as shape, size, and surface modifications (e.g., charge, oligonucleotide, ligand arrangement, specific receptor, and cell-penetrating peptide), play crucial roles in their interactions with cell membranes. Given the numerous bio-applications of nanoparticles, a systematic understanding of interactions between nanoparticles and cell membranes is of great significance. Numerous articles have demonstrated that positively charged nanoparticles excel in penetrating cell-membrane barriers. In contrast, nanoparticles with neutral surface coatings, such as polyethylene glycol, exhibit reduced

interaction with cell membranes, resulting in minimal cell internalization[7].

In recent years, various chemical methods have been developed to synthesize functionalized nanoparticles specifically for applications such as drug delivery, cancer therapy, diagnostics, tissue engineering, and molecular biology. The structure-function relationship of these functionalized nanoparticles has been extensively examined. With the growing understanding of methods to functionalize nanoparticles, along with the ongoing efforts of innovative scientists to advance this technology, functionalized nanoparticles will likely become a significant tool in the aforementioned areas [8].

Over the years polymeric nanoparticles have been used to deliver the drug to the cancer cells. The small size of nanoparticles allows them to sneak through the leaky vessels of the tumour and the faulty lymphatic drainage system ensures that the nanoparticles reside in the tumour for a prolonged time. This effect is collectively known as the Enhanced permeability and retention (EPR) effect.[9] Nanoparticles offer various benefits in cancer treatment, which include improved penetration of drugs across the cell which improves the drug delivery, improved pharmacokinetics of drugs, enhanced treatment efficiency, and tailored designs to enhance the drug delivery to specific sites by using various ligands. This also ensures targeting the drug to the specific site and thus reducing side effects.

There are various approaches to deliver drugs to the cancer cells one of the most promising being surface functionalization of the nanoparticles with a targeting ligand. These ligands have site-specific activity, which ensures that the nanoparticles are targeted to the cancer cell thus enhancing the treatment efficacy and reducing the side effects. Surface functionalization of nanoparticles helps us to achieve targeted drug delivery, improved pharmacokinetics and bioavailability, and modifiable release of drugs through nanoparticles.

SURFACE FUNCTIONALIZATION OF NANOPARTICLES:

Polymeric nanoparticles are one of the promising platforms for targeting drugs to cancer cells as they can be available from various sources, moreover, their molecular weight and physicochemical properties can be modified. Additionally, many polymers are biocompatible and biodegradable and have established safety profiles after being subjected to clinical trials and post-market surveillance studies. Various researchers have been intensively working towards the improvement of polymeric nanoparticles to achieve efficient drug targeting [10-12].

Active targeting of nanoparticles to the tumour cells involves conjugating targeting ligands to the nanoparticles which then explicitly bind to overexpressed receptors and thus induce activity on the target cell [13]. Nanoparticles can be functionalized which involves modifying the surface chemistry of the particles and allows for the conjugation of ligands (small molecules, antibodies, and peptides). Various approaches have been designed to target polymeric nanoparticles to the desired site of activity with the use of targeting ligands. Different methods that are used for surface functionalization are given in Fig 2.

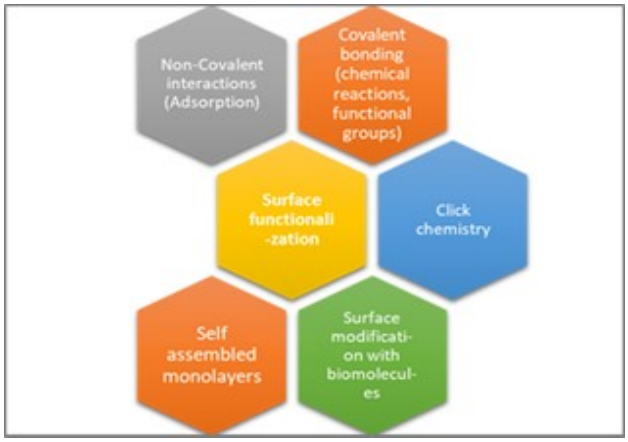

Fig 2. Surface functionalization of nanoparticles.

Once the nanoparticles are surface functionalized the targeting ligand interacts with the receptor and induces internalization of the nanoparticles and eventually achieves drug release within the cell via receptor-mediated endocytosis [14,15].

Antibodies as targeting ligands:

Antibodies also termed immunoglobulins are glycoproteins that are expressed on the B cell's surface acting as antigen receptors. These can work as therapeutic agents or targeting ligands, but conjugated antibodies have drawn much attention as they are more suitable for site-specific targeting which improves their potential to treat cancer [16,17]. IgG antibody is the most widely used antibody to surface functionalize nanoparticles [18,19].

Methods of surface functionalization:

Surface modification of nanoparticles can be achieved by various mechanisms like conjugation, adsorption, etc. to target the drug to the desired site of action [20].

***Adsorption*:**

Adsorption is a non-covalent interaction process that consists of physical adsorption and ionic binding [21]. In this process, the targeting ligand is attached to the nanoparticles through weak interactions such as electrostatic, hydrogen bonding, hydrophobic, and van der Waals attractive forces [22]. Ionic bonding occurs when oppositely charged targeting ligands and nanoparticles interact through ionic linkage [23]. The method of ionic absorption has been demonstrated in Fig 3.

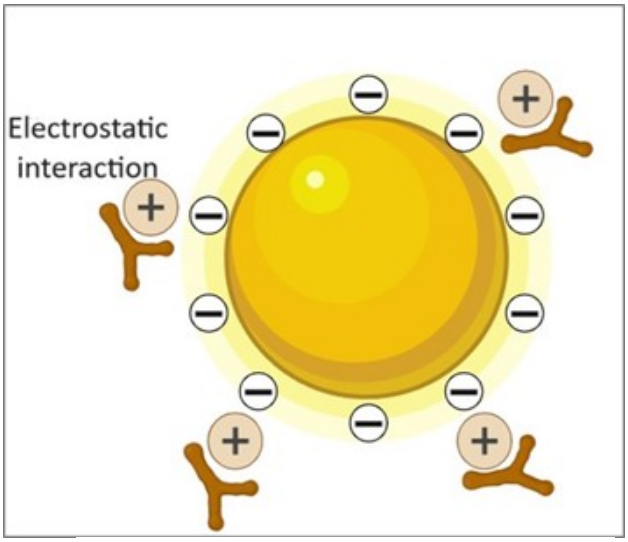

Fig 3. Surface functionalization by ionic interaction.

***Covalent binding*:**

Surface functionalization of nanoparticles with a targeting moiety by covalent bonding involves attaching the targeting moiety to the surface of nanoparticles by chemical reactions. The most common covalent binding processes are carried out either by carbodiimide interactions or click chemistry. Surface functionalization by the covalent binding process offers greater stability and ensures better reproducibility of the formulation [24].

***Carbodiimide interactions*:**

During the covalent binding process nanoparticles containing aldehydes, cyanogen bromide or epoxides can easily react with the amino group of the targeting ligand e.g. the amide group of antibody IgG can react with the nanoparticles having reactive species as mentioned above on their surface to form a covalent bond [25,26]. However, when the surface of nanoparticles contains a carboxyl group, the surface needs to be activated using a cross-linking agent like 1-ethyl-3-(-3-dimethylaminopropyl) carbodiimide (EDC), which reacts with the amide group of the targeting ligand. This results in forming a bond between the nanoparticle and the targeting ligand. Such a reaction is possible due to the use of carbodiimide and the interaction thus is known as carbodiimide chemistry. It is a water-soluble compound that is used to form bonds between carboxyl or phosphate group and primary amines [27,28,29]. The use of N-Hydroxysuccinimide (NHS) or N-Hydroxysolfosuccinimide (Sulfo-NHS) during crosslinking may be useful in cases where the targeting ligand contains both amine and carboxyl group, as the reaction step is increased due to addition of NHS or Sulfo-NHS which prevents intermolecular and intramolecular crosslinking of such targeting ligands [30-31].

***Click chemistry*:**

It refers to a group of chemical reactions with orthogonality, site-specificity, and favorable reaction rate. These can occur at room temperature, under mildly reactive aqueous solvents. These require no or minimal purification. As a result, irreversible chemical bonds are obtained and cytotoxic byproducts are absent [32-25]. "Click" reactions include: i) cycloaddition reactions, namely 1,3-dipolar (*e.g.* copper (I)-catalyzed [3 + 2] azide-alkyne cycloaddition (CuAAC) reaction and strain-promoted [3 + 2] azide-alkyne cycloaddition (SPAAC) reaction) and hetero Diels-Alder (*e.g.* inverse electron demand [4 + 2] Diels-Alder (iEDDA) reaction); ii) Staudinger ligation; and iii) "Thiol-ene" reaction [36].

- Azide–alkyne cycloaddition (CuAAC reaction):

In this reaction surface functionalization of nanoparticles is carried out by the interaction of azide group. Once surface functionalization has taken effect the azide group is reacted with the alkyne group in the presence of a copper catalyst to form a triazole ring. [37,38].

- Strain-promoted azide-alkyne cycloaddition (SPAAC Reaction):

In this reaction, the nanoparticles are surface functionalized with the azide group and when the surface functionalization has taken place the azide groups are reacted with strained alkynes (cycloalkynes) to create stable triazole. This reaction does not need a copper catalyst; hence it is useful to eliminate copper toxicity [39-41].

- Diel's Alder reaction:

This reaction is faster than CuAAC and SPAAC reactions. This reaction is also called inverse electron demand Diel's Alder reaction. It involves a reaction

Table 1. Application for surface functionalization.

Application	Nanoparticle type	Surface functionalization	Mechanism/function	Study
Targeted drug delivery [10]	liposome	PEGylation with antibody	Enhances circulation time and targets specific tumor cells through receptor-mediated endocytosis	HER2-targeted liposomal doxorubicin shows improved uptake in HER2-positive breast cancer cells.
	Gold nanoparticles [43]	Folate conjugation	Targets folate receptor-overexpressing cancer cells, enabling selective drug delivery.	Folate-conjugated gold nanoparticles enhance the delivery of paclitaxel to ovarian cancer cells.
	PLGA nanoparticles [44,49]	Aptamer functionalization	Aptamers target specific cancer cell surface markers, facilitating drug delivery to malignant cells.	PLGA nanoparticles functionalized with aptamers deliver cisplatin specifically to prostate cancer cells, reducing toxicity to healthy cells.
Controlled Release [45]	Mesoporous silica	pH-sensitive polymers	Releases drug in acidic tumor microenvironments, providing controlled and site-specific drug delivery.	Doxorubicin-loaded mesoporous silica nanoparticles release the drug selectively in the acidic environment of tumor cells, minimizing systemic toxicity.
	Polymeric nanoparticles [46]	Temperature sensitive polymer	Releases drugs in response to hyperthermic conditions, providing on-demand drug release at tumor sites.	Poly(N-isopropyl acrylamide)-)-coated nanoparticles release paclitaxel at temperatures above physiological levels, enhancing the therapeutic index.
Gene Delivery [48]	Lipid nanoparticles	Cationic lipid functionalization	Facilitates the delivery of genetic material, such as siRNA or DNA, to target cancer cells, silencing oncogenes or delivering therapeutic genes.	siRNA-loaded cationic lipid nanoparticles effectively silence genes involved in cancer cell proliferation, demonstrating potential in gene therapy for cancer treatment.
Multimodal Therapy [48]	Iron oxide nanoparticles	Conjugation with chemotherapeutic agents and dyes	Combines imaging and therapy (theragnostic) to provide real-time monitoring of drug delivery and therapeutic response, enhancing treatment precision and personalization.	Iron oxide nanoparticles conjugated with doxorubicin and near-infrared dyes enable simultaneous drug delivery, MRI, and photothermal therapy in breast cancer models, showing enhanced therapeutic outcomes.
	Gold nanoparticles [49]	PEGylation and conjugation with photosensitizers	Enables photothermal therapy by converting light energy into heat to ablate cancer cells, in combination with drug delivery for synergistic effects.	PEGylated gold nanoparticles conjugated with photosensitizers and chemotherapeutic agents are used for combined photothermal and chemotherapy in treating melanoma, improving efficacy.

between Diene and dienophile where the surface of nanoparticles is functionalized with diene or dienophile and a cycloaddition reaction is performed between diene and dienophile to get a six-membered ring [42].

Applications of surface-functionalized nanoparticles:

Table 1 gives an insight into various applications of surface-functionalized nanoparticles for cancer treatment.

CONCLUSION:

Nanoparticle delivery systems represent a transformative advancement in drug delivery, particularly in the context of cancer treatment. The ability to manipulate the size, surface characteristics, and release profiles of nanoparticles has opened new avenues for targeted therapies, allowing for site-specific drug delivery that enhances therapeutic efficacy while minimizing adverse

effects. Surface functionalization of nanoparticles plays a crucial role in optimizing their performance. Techniques of surface functionalization not only improve the targeting accuracy of nanoparticles but also enhance their stability, biocompatibility, and overall effectiveness. The application of functionalized nanoparticles in cancer therapy has shown significant promise, particularly in overcoming challenges such as drug resistance and off-target effects. By exploiting the Enhanced Permeability and Retention (EPR) effect and utilizing targeting ligands, these nanoparticles can preferentially accumulate in tumour tissues, providing sustained and controlled drug release. As research in nanoparticle functionalization continues to evolve, these technologies will likely become increasingly integral to precision medicine. The ongoing development of innovative functionalization techniques and the expanding understanding of nanoparticle-cell interactions suggest a future where nanoparticles can be tailored to meet the specific needs of individual patients, ultimately leading to more effective and personalized treatment strategies in oncology and beyond.

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