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Review Article

Challenges and Issues with Development of Drug Nanoparticles

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ABSTRACT

Due to the unique or superior physico-chemical properties compared to bulk material, nanoparticles have become extremely popular in recent years. The pharmacokinetic and pharmacodynamic properties of many different types of therapeutically active compounds have been remodified and improved by using particle systems like nanoparticles. A safe targeted drug delivery could improvise the performance of some therapeutically active agents already on the market and moreover will have implication for the development and success of new therapeutic strategies such as anticancer drug delivery, protein and peptide delivery and the development of nanoscale drug delivery devices. The current connections integrate on in-depth knowledge of nanoparticles with respect to formulation aspects, types, preparation and stability issues and challenges. This review article focuses on the potential of nanotechnology in medicine and discuss about the different nanoparticulate drug delivery systems as well as the application in therapy. Because of its great selectivity towards the target region, it is used significantly in the field of administering drug substances as it can limit the potentially toxic effects of drugs on normal cells. Nanoparticles play a significant character and conjugate with diverse therapy using exact methods to deliver the drug to target sites.

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INTRODUCTION

Nanoparticles can solve and compensate for some of the most significant limitations of chemotherapy, namely its lack of specificity and narrow window of therapeutic efficacy [1-3]. High surface area to mass ratio, small size of nanoparticles special chemical and physical properties and various morphology of particles are some positive prints about nanotechnology [4,5]. Nanoparticles are colloidal carriers with dimension on nanoscale(10^{-9}m) [6]. Nanoparticles exhibit unique physicochemical properties distinct from their bulk counterparts owning to their high surface area to volume ratio and quantum effects. Nanotechnology offers potential developments in pharmaceuticals, medical imaging and diagnosis, cancer treatment, implantable materials, tissue regeneration and even multifunctional platforms combining several of those modes of action into packages a fraction size of a cell [7,8]. In regenerative medicine, nanomaterials can be used as scaffolds for tissue engineering or as carriers for growth factors and other signalling molecules that promote tissue repair and regeneration It can be correctly envisioned as the future of drug delivery technology as they have the potential to become useful therapeutic and diagnostic tools in potential to become useful therapeutic and diagnostic tools in the near future to shorten the gap between the drug discovery and drug delivery[9,10]. The most promising part is nanomedicine where nanoparticle-based imaging and therapy have shown the potential for unparallel performance over conventional tools [11]. Additionally, nanoparticles can be designed to release their cargo in a controlled manner, allowing for sustained drug delivery over time. The allure of nanoparticles lies in their versatility, manifesting in applications spanning diverse domains, including medicine, electronics, environmental remediation, and catalysis, among others [12].

APPLICATIONS

Nanoparticles have better stability than liposomes. This characteristic is very important for various modes of targeting. It is also used in colloidal drug delivery system which is biodegradable and can stored for at least one year. Application of nanoparticle in ophthalmic drug delivery. Common polymers are used for synthesis of ophthalmic nanoparticles are poly alkyl cyanoacrylates. The pH of the

polymerization medicine should be remained below three [13-16].

Clinical applications of nanoparticles in ophthalmia in future. The anti-oxidant biosensor may have clinician to recognise patients need therapy before clinical manifestation of critical disease are obvious and tissue damage happen [17-18]. By combining therapeutic genes (like catalyse, peroxidase, superoxide, dismutase) to the ARE, we could make a combine therapeutic diagnostic as an alternate of reporter gene like GFP [19]. Some medical applications of nanomaterials like imaging, diagnostic, and treatment nanoscale drug delivery systems can enhance the performance [20].

Nanoparticle based catalyst used in clean up pollutant and contaminants and nano filtrate that are used to purify contaminated water, air, and soil by reducing pathogens and pollutants [21].

ADVANTAGES

Enhanced strength and durability nanoparticle drug carriers have higher stability. It helps in achieving higher therapeutic response with lesser adverse effects. It is also used in cosmetic since it absorbed deeper into the skin and are used to deliver medicines since it is absorbed effectively [22].

LIMITATIONS

It has limited drug loading. Controlling of nanoparticles is difficult in liquid and drug forms. Nanoparticles may form toxic metabolite and it is much expensive. Nanoparticle could Dipo site in organisms over time. Easy inhalation of nanoparticle resulting in lung diseases [23].

CLASSIFICATION OF NANOPARTICLES

Here are the different types of nanoparticles classified below:

A. Carbon-based nanoparticles

Carbon based nanoparticles are break into carbon nanotube and fullerenes. They are 100 times stronger than steel. Carbon nanotubes can be divided into single walled carbon nanotubes (SWCNTS) and multiwalled CNTS. CNTS are thermally conductive along the length and non-conductive across the tube. Fullerenes are carbon allotropes have hollow cage structure of 60 carbon atoms or more [24].

B. Ceramic nanoparticles

These nanoparticles are inorganic composed of oxides, carbides, carbonates and phosphates. These nanoparticles have high heat resistance and have chemical inertness. They are used in photocatalysis, photodegradation of dyes and biological imaging. Most important application of

CN is in drug delivery. They are used effectively as a drug delivery system for various diseases like bacterial infections, cancer and glaucoma [25].

C. Metal nanoparticles

It is prepared from metal precursors. It is synthesised by photochemical, electrochemical, and chemical methods. In chemical methods, the metal nanoparticles a synthesized by reducing the metal ion precursor in solution with reducing agents. The obtained nanoparticles absorb small particles as they have high surface energy. Different types of metal nanoparticles are silver, gold, titanium, copper, zinc, palladium etc.

It is used across various research fields, including imaging and detection of biomolecule, and are widely used across drug delivery [26].

D. Semiconductor nanoparticles

These are materials which is built at the level of nanoscale. They compromising elements from the periodic groups II-VI, III-V, or IV-VI with diameter in the range 1-12nm. Semiconductor nanoparticles are classified into four types-

Zero Dimensional

Quasi one Dimensional

Two Dimensional

Three Dimensional

Semiconductor nanoparticles are involved in application of photocatalysis, nanoparticles, electronic devices, and water splitting. Current day devices like computers, cell phones, television remote controls, satellite dishes and Fiber network also contain semiconductor nanoparticles [27-28].

E. Polymeric nanoparticles

These are the organic based nanoparticles. The size range of polymeric nanoparticles from 1 to 1000nm. These are based on the preparation method as these have structure shaped like nanosphere as nano capsules. A nanosphere nanoparticle has a matric like structure which nano capsules have core shell anatomy [29]. In nanosphere polymeric nanoparticles, the active compounds and the polymer are identically distributed while the nano capsule nano particles the active compounds are restricted and surrounded by a polymer shell.

Some of the advantages of these involves controlled release, protection of drug molecule since they move between the internal and external environment. Polymeric nanoparticles are used in drug delivery and its diagnostic use. Also, these nanoparticles have the benefit of highly

biodegradable and biocompatible in drug delivery systems [30].

F. Lipid nanoparticles

Lipid nanoparticles are spherical in shape of diameter from 10 to 100nm. Their structure composed of a solid core which is made up of lipid and a matrix consisting soluble lipophilic molecules. These types of nanoparticles are used in the biomedical field such as drug carrier and RNA release in cancer therapy [31].

Table 1. Advantages and limitations of nanocarrier systems

Nanocarrier	Advantages	Limitation
Liposomes	Ability to carry either, hydrophilic or hydrophobic drugs, biocompatible, biodegradable, stable, possibility of surface functionalization	Toxic because the drug can be leaked or displaced into the blood stream; high production cost.
Polymeric nanoparticles	Biocompatible, low toxicity, biodegradable, cost-effectives, possible surface functionalization, avoids leakage of the drug.	Difficult to scale up
Solid Lipid Nanoparticles (SLNs)	Protect drug against harsh environmental conditions, easy scale up, biocompatible.	Low drug loading efficacy due to its crystalline structure, there is a chance of drug expulsion during the storage of the crystalline structure and initial burst release can occur
Nano emulsions	Stable, Carry both hydrophobic and lipophilic drugs	Toxicity of surfactants
Metallic nanoparticles	Antibacterial, antifungal properties, stable, uniform structure	Toxicity

METHODS OF PREPARATION

Methods used for nanoparticles preparation are of the following types-

1. According to polymerization,
   i. Emulsion polymerization

ii. Dispersion polymerization
iii. Interfacial polymerization
iv. Interfacial complexation

2. According to cross linking method,
   i. Heat-cross linking
   ii. Chemical cross linking
3. According to Polymer precipitation method,
   i. Solvent evaporation method
   ii. Double emulsion method
   iii. Emulsion diffusion method
   iv. Salting out method

Preparation of nanoparticle by polymerization-based method

i. Emulsion polymerization

Emulsion polymerization involves emulsions containing water, monomers, and surfactants. Oil-in-water emulsions are the most common type of polymerization emulsion in which monomer droplets are emulsified in water in successive stages. Emulsion polymerization is one of the fastest methods for preparing nanoparticles. It involves dispersing monomers in a solvent (non-solvent) in which they do not dissolve. Surfactants or insoluble polymers are used to prevent aggregation in the early stages of polymerization. The polymerization process can be initiated by different methods, such as the application of radiation such as ultraviolet or visible light, and monomers can be converted to initiate free radicals. Initiation occurs when monomers collide with free radicals. Phase separation and material formation may occur before or after the termination of the polymerization reaction [32].

ii. Dispersion polymerization

It involves the formation of a homogeneous process when monomers, initiators and stabilizers are dissolved in a solvent, thus forming a polymer. In this way, monomers and initiators are easily dissolved in the solvent used in the reaction environment, but the solvent is not a solvent. It induces nucleation directly in aqueous solution. monomer solutions. Initiation occurs by high-energy electricity of the same mechanism as emulsion polymerization. Polymerization is initiated by the addition of the catalyst and continues with the nucleation step. In the case of dispersion polymerization, monomers are not emulsified but dissolved in an aqueous medium that acts as a precipitating agent for subsequent polymer formation [33]. In this type of polymerization, the presence of surfactant stabilizer is not necessary to form stable nanospheres. This method was used to prepare biodegradable polyacrylate and

polymethylmethacrylate (PMMA) nanoparticles.

iii. ***Interfacial polymerization***

It is a sequential polymerization in which polymerization occurs at the interface of two immiscible phases (usually two liquids). Making nanoparticles is a good idea [34]. It involves the polymerization of two reactive monomers or reagents dissolved in two phases (e.g., continuous phase and dispersed phase), and the reaction occurs at the interface of the two liquids. Oil-containing nano capsules are obtained by polymerization of monomers of oil/water mixtures of perfect oil-in-water microemulsions. The process is based on microencapsulation process. In the case of preparation of nanoparticles with the help of surfactants, aqueous polyelectrolyte solutions are carefully dissolved in reverse micelles of the non-polar bulk phase. Competitive polyelectrolytes are added end mass, allowing a layer of polyelectrolyte complexes to copolymerize at the interface [35].

Preparation of nanoparticle by cross linking technology

These nanoparticles are prepared from amphiphilic macromolecules, proteins and polysaccharides with good affinity for water and lipid solvents. The preparation process involves the assembly of amphiphiles followed by stabilization by thermal denaturation or chemical coupling. It involves the emulsification of bovine serum albumin/human serum albumin or aqueous protein solution to dissolve it in oil using high homogenization or high frequency sonication. Pour the anhydrous emulsion into the preheated oil (thermal crosslinking). Keep the suspension in preheated oil above 100 degrees Celsius, stirring continuously for a while to denature and collect the protein content and evaporate the water. The results were washed with natural solvents to remove traces of oil and collected by centrifugation. Chemical crosslinking is done for heat sensitive products [36].

Preparation of nanoparticle by polymer precipitation method

i. Solvent evaporation

In this method, the polymer is dissolved in organic solvent such as chloroform, methylene chloride and then the drug is dispersed in the solution. This mixture is then emulsified in an aqueous phase containing surfactants such as surfactants. Sodium dodecyl sulfate. Oil-in-water emulsions are formed with the help of mechanical mixing, ultrasonic treatment, or micro fluidization (high-pressure homogenization). The organic weight is

then evaporated by increasing the temperature and decreasing the pressure with constant stirring. The size of nanoparticles can be controlled by adjusting the mixing speed, type and amount of dispersant, viscosity of the organic and aqueous phase, and temperature [37]. The polymers used in this method are PLA, PLGA, cellulose acetate phthalate, poly beta-hydroxybutyrate (PHB).

ii. Double emulsion method

This method is designed for combining hydrophilic substances, because emulsification and evaporation methods have poor encapsulation of hydrophilic substances, so double emulsification technology is used. In this way, W/O emulsion is prepared by adding aqueous solution to the organic polymer solution with constant stirring. The prepared emulsion was added to another aqueous phase, mixed to obtain a w/o/w emulsion, and then the organic solvent was removed by high-speed centrifugation [38].

iii. Emulsion diffusion method

It is an improved version of the solvent evaporation method. This method is another way to avoid heavy weight problems caused by the emulsion evaporation method. It is easy to use and reproduce. It is also used to encapsulate many drugs, including peptides and proteins. In this way the encapsulating polymer is dissolved in a portion of the water-soluble solvent (e.g. propylene carbonate) and saturated with water to provide an initial thermodynamic equilibrium between the two liquids. Next, the polymer-water-saturated solvent phase is emulsified in an aqueous solution containing a stabilizer that causes the solvent to migrate into the semi-external phase and form nanospheres or nano capsules, depending on the oil to polymer ratio. Finally, the solvent is removed by evaporation or filtration, depending on its boiling point [39].

iv. Salting out method

The salting method is an improved version of the emulsification diffusion method. The polymer and drug are initially dissolved in the solvent. In this way, toxic solvents are not used. Acetone is often used because it is miscible with water and easy to remove. The above mixture is then emulsified into a water gel containing electrolytes, magnesium chloride, calcium chloride and non-electrolyte salt solutions such as magnesium acetate or sucrose. Dilute the oil/water emulsion with sufficient water or aqueous solution to increase the diffusion of acetone into the aqueous phase to trigger the formation of

nanospheres. Salting does not require high temperatures and therefore will be useful in cases where electrical devices are required. Its major disadvantage is that it can only be applied to lipophilic substances and requires the use of extensive nanoparticle purification techniques [40].

EVALUATION OF NANOPARTICLES

Evaluation of nanoparticles can be tested through the following parameters:

Yield of Nanoparticles

Nanoparticle yield is determined by comparing the total weight of the nanoparticles formed with the total weight of the copolymer and drug.

(% yield amount of nanoparticle amount of drug + polymer 100)

Drug Content / Surface entrapment/ Drug Entrapment

It is the drug content/drug trapped on the surface/embedded within the drug. The amount of drug present after centrifugation is determined by UV spectrophotometry in the supernatant liquid (w). The amount of drug (W) present in the supernatant is subtracted from the total amount used in the nanoparticle preparation i.e., (W-w) [41]. is the drug Encapsulation Efficiency Calculation Formula:

% Drug Entrapment= Actual Content/ Theoretical content x 100

Particle Size and Zeta Potential

Particle size and Zeta potential Use the Malvern Zetasizer to determine the particle size and Zeta potential value of the prepared nanoparticles.

Surface Morphology

The surface morphology of the prepared nanoparticles was examined by scanning electron microscope (SEM).

Polydispersity index

The polydispersity index of the prepared nanoparticles was measured using Malvern Zeta sizer [42].

Kinetic Study

In vitro drug release studies were performed at 50 rpm in a USP Type II dissolution apparatus. Place the container in 900 mL of phosphate buffer solution and maintain the temperature at 37 ± 0.20 °C. Remove the required 5ml of medium at a certain time and transfer the same volume of dissolution medium into the flask to maintain constant volume. Expand the extracted sample using a UV spectrophotometer [43].

Stability of Nanoparticles

To determine the stability of the prepared nanoparticles, the study was carried out by keeping the preparation in a stable room between 4°C ± 1 ºC and 30 ºC ± 2 ºC for 90

days. Analyse samples after a certain period of time, such as changes in drug content, drug release rate (t_{50} %) and appearance at 0, 1, 2 and 3 months [44].

BASICS OF STABILITY

In aqueous suspension, metal oxide nanoparticles are of two types-

A) Kinetic stability

Energy barrier (DLVO theory), dispersion, aggregation, flocculation

B) Thermodynamic stability

Minimization of surface energy, Ostwald ripening (dissolution reprecipitation). It is possible to ignore the ripening of nanoparticle in suspension and to check their dimension by observing the precipitation conditions. When the pH precipitation is enough far from the point of zero charge and the ionic strength in enough high, the ripening of nanoparticles is ignored. Zero interfacial tension is defined the stability condition correlate to the electrostatic and chemical saturation of the water oxide interface. In such condition, charge surface groups density reaches its higher, the interfacial tension its lowest and later adsorption forces the surface area to increase in size and as a result, the size of nanoparticles decrease [45].

STABILITY ASPECTS OF NANOPARTICLES

i. Physical Aspects

a. ***Particle size, size distribution and morphology***

Particle size and size distribution are fine important parameters that are used to determine the physical stability of nanoparticle.

A various technique that is used to determine the particle size and size distribution like photon correlation spectroscopy also called as dynamic light scattering, laser diffraction and coulter counter. The DCS/DLS is mostly used to evaluation the size and size distribution of tiny particles suspended in liquid medium. The measured parameter of this technique are the mean particle size and size distribution known as poly dispersity index. Value of PDI is 0.1 to 0.25 indicates a narrow size distribution whereas a PDI higher than 0.5 indicates to a road distribution [44]. However, this technique is not able to determine the size of dry powders. LD is best used in combining with PCS.

b. *Sedimentation*

The older method to determine sedimentation creaming is visual observation over a period of time.

By determining the volume of the resolved on creamed particle layer relative to the total suspension in a relative to the total suspension in a particular time. Flocculation volume is a dimensionless parameter which can be obtained as a quantitation evaluation of suspension stability. More flocculation volume shows more stable suspension [45].

c. ***Particle surface charge***

Laser Doppler electrophoresis is mostly used to determine zeta potential. This technique determines the electrophoretic movement of particles in the medium. General rule is the value of the ZP more than 60mv produces good stability whereas 30, 20 and less than 5 mv yields lower stability than 60 mv. This rule is only applicable for pure electrostatic stabilization and is not applicable when high molar mass stabilizers are present.

d. ***Crystalline state***

The crystallinity of drug nanoparticles is evaluated by X-ray diffraction and differential scanning colorimetry. XRD distinguish amorphous and crystalline nanoparticles also different polymorphic phases of the particles, whereas DSC is usually used as a supplementary tool to XRD. Crystalline particles mostly have a sharp melting peak. The melting point also used to differentiate various polymorphs. [46]

ii. **Chemical aspects**

HPLC is the common technique used to determine chemical stability. HPLC provides accurate quantitative analysis on the degradation impurities. Mass spectroscopy is usually combined with HPLC to recognised the molecular structure of impurities.

FTIR and NMR are other techniques that are used chemical stability assessment but they are not as accurate and sensitive as HPLC and mostly used for stability assessment.

Several factors influence the chemical stability of nanoparticles:

a. ***Material selection***

Choosing stable materials such as polymers, lipids, or inorganic compounds with inert properties can enhance the chemical stability of nanoparticles.

b. ***Surface modification***

Functionalizing nanoparticle surfaces with stabilizing agents or coatings can protect against chemical degradation and improve stability.

c. ***Storage conditions***

Proper storage conditions, including temperature, humidity, and light exposure, are essential for maintaining the chemical stability of nanoparticles. Storing nanoparticles in inert atmospheres or under vacuum can also minimize degradation.

d. ***pH Sensitivity***

Some nanoparticles may exhibit pH-dependent stability, with potential degradation in acidic or basic environments. Designing nanoparticles with pH-responsive materials or coatings can mitigate this issue.

e. ***Oxidative stability***

Nanoparticles may be susceptible to oxidation, particularly metal-based nanoparticles. Using antioxidants or incorporating stabilizing agents can protect against oxidative degradation.

f. ***Drug interaction***

Nanoparticles loaded with drugs may undergo chemical interactions with the drug molecules, leading to degradation or loss of activity. Understanding these interactions and optimizing formulation parameters can enhance stability.

g. ***Manufacturing processes***

Controlling manufacturing processes and minimizing exposure to harsh conditions such as high temperatures or reactive chemicals can improve the chemical stability of nanoparticles.

h. ***Characterization***

Regular characterization of nanoparticles is essential for assessing their chemical stability over time.

THERAPEUTIC STRATEGIES OF NANOPARTICLES

Therapeutics Targeted therapy in disease treatment is the approach of delivering appropriate amounts of therapeutic agent for a prolonged period to the affected area within the body. To achieve this, development of safer and more effective therapeutic nanoparticles is crucial and one of the ultimate goals of nanomedicine [47]. As soon as nanoparticles enter to the bloodstream, they are prone to aggregation and protein opsonization (protein binding to nanoparticle surface as a tag for immune system recognition).

Therapeutic strategies of nanoparticles are used in drug delivery system, cancer therapy, dense desmoplastic stroma in PDAC and for immune-modulation.

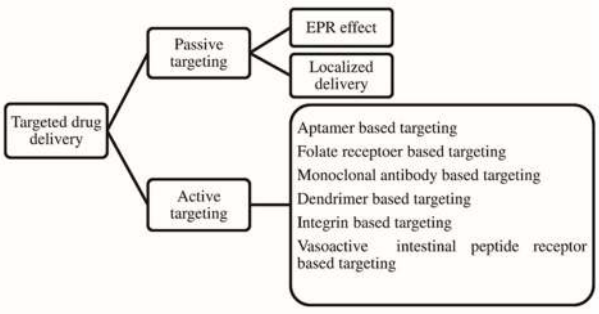

Figure 1: Classification of Targeted DDS

Designing of nanoparticles for drug delivery system

Choose biocompatible and biodegradable materials such as polymers (e.g., PLGA, PEG), lipids, or inorganic materials (e.g., gold, silica) based on the desired properties and intended application. Optimize the size and shape of nanoparticles to achieve desired drug release kinetics, circulation time, and cellular uptake. Smaller particles generally exhibit better tissue penetration, while specific shapes may enhance targeting capabilities [48]. Functionalize nanoparticle surfaces with ligands, antibodies, or peptides to enable targeting of specific cells or tissues, as well as to improve stability and biocompatibility. Encapsulate the drug within the nanoparticle matrix or conjugate it to the surface, ensuring controlled release and protection of the drug from degradation. Incorporate stimuli-responsive or sustained-release mechanisms into the nanoparticle design to achieve controlled drug release profiles, triggered by factors such as pH, temperature, or enzymatic activity. Characterize the physicochemical properties of the nanoparticles, including size, shape, surface charge, drug loading capacity, and release kinetics, using techniques such as dynamic light scattering, electron microscopy, and spectroscopy.

Assess the cytotoxicity, cellular uptake, pharmacokinetics, and therapeutic efficacy of the nanoparticles using cell culture models and animal studies to ensure safety and efficacy. Develop scalable manufacturing processes for producing nanoparticles reproducibly and in large quantities while maintaining quality and consistency [49]. Consider regulatory requirements for nanoparticle-based drug delivery systems, including safety assessments, preclinical studies, and approval processes for clinical trials and commercialization.

Limitations of Nanoparticles in Drug Delivery System

Biocompatibility and Toxicity

Certain nanoparticle materials may elicit immune responses or toxicity in the body, leading to adverse effects. Understanding and mitigating these effects are essential for safe clinical translation.

Off-target effects

Despite efforts to target specific cells or tissues, nanoparticles may still accumulate in unintended sites, leading to off-target effects and potential toxicity.

Clearance and Metabolism

Nanoparticles may be rapidly cleared from the bloodstream by the immune system or metabolized by enzymes, reducing their circulation time and therapeutic efficacy.

Complex manufacturing processes

The production of nanoparticles for drug delivery often involves complex and expensive manufacturing processes, limiting scalability and increasing costs.

Storage and Stability

Nanoparticles may exhibit instability during storage, leading to aggregation, degradation, or loss of drug payload, which can affect their efficacy and shelf life.

Immunogenicity

Some nanoparticle formulations may trigger immune responses, leading to inflammation or immune rejection, particularly upon repeated administration.

Batch-to-Batch Variability

Variability in nanoparticle size, shape, and surface properties between batches can affect their performance and reproducibility, posing challenges for clinical development and regulatory approval.

Limited cargo capacity

Nanoparticles may have limited capacity for loading therapeutic agents, particularly large molecules or multiple drugs, restricting their versatility in certain applications.

Regulatory hurdles

Nanoparticle-based drug delivery systems may face regulatory challenges related to safety, efficacy, and manufacturing processes, which can prolong the approval process and increase development costs.

Nanoparticles designed to address dense desmoplastic stroma in PDAC

Pancreatic tumours are characterized by their characteristic desmoplastic stroma, which accounts for 80 % to 90 % of tumours. The complex matrix consists of cellular components such as cancer fibroblasts (CAFs), pancreatic stellate cells (PSCs), and differentiated anti/pro-tumour cells. Non-cellular components are also part of the matrix with more extracellular matrix (ECM) such as collagen, fibrinogen, hyaluronic acid (HA), and various chemokines and cytokines [50].

Nanoplatform designed for immune-modulation and improved immunotherapy

Immunotherapy techniques involve reprogramming the immune system to recognize and destroy malignant cells. The goal is to restore the essence of cancer prevention through a medical system that supports the expansion, activation, commercialization and functioning of specific cancer cells.

Nanoparticles deigned to address the anti-cancer therapy

Nanoparticles drug delivery systems have provided the alternative method for improving the therapeutic potential of various agents and bioactive molecules through the Enhanced Permeability and Retention (EPR) effect. Worldwide cancer is one of the leading causes of death. Various versatile nano formulations such as micelles, liposomes, nanoparticles, and nano emulsions with excellent biocompatibility and pharmacokinetic properties have exhibited great potential for the delivery of novel anticancer drugs Figure 2 [51]. By encapsulating specific therapeutic agents in nanocarriers can achieve satisfactory tumour targeting by utilizing the EPR effect mediated passive targeting strategies; and active targeting can be achieved by conjugating nanomedicines with ligands that can specifically target overexpressed receptors on the tumour cells.

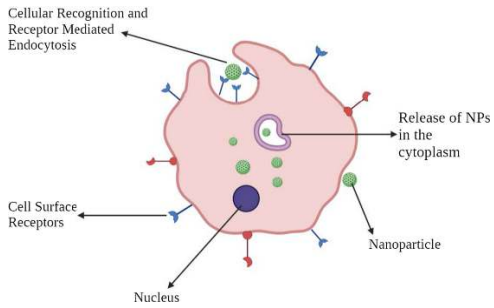

Figure 2: Active Cellular Targeting

Receptor-mediated active targeting strategy

To overcome the TME (Tumour Micro Environment) barriers and deliver pharmaceutical active ingredients to the tumour sites by either passive or active targeting strategies, nanoparticles can be used Figure 2. In Passive targeting strategies, the transport of nanoparticles through the leaky tumour vasculature-mediated EPR effect, leading the nonspecific tumour accumulation. In Active targeting strategies, specialized chemical ligands can be conjugated to the surface of nanoparticles to deliver the medication to the specific targeting tumour cell [52]. The encapsulated therapeutic agent nanoparticles by binding to a specific receptor can be effectively taken up into tumour cells through receptor- dependent endocytosis.

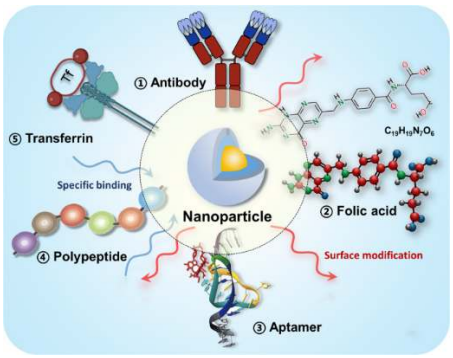

Figure 3: Tumour Specific target modifications of smart nanoparticles[53].

Some approaches are summarized for utilizing cell surface active targeting strategies for advanced tumour treatment, in the following sections:

i. **Epidermal Growth Factor Receptors (EGFRs) – based active targeting**

It includes in several types of cancers, including lung, pancreatic, colorectal and breast cancers. Activation of EGFR triggered by binding of ligands, including EGF, transforming growth factor-α (TGF-α), epiregulin, heparin binding EGF, betacellulin, amphiregulin and neuregulin G2β. Nan and co-workers prepared versatile nanoplatforms for specific codelivery of DOX and cisplatin to tumour sites by utilizing an EGFR-targeted approach. Liang et al. prepared versatile nanoplatforms for lesion-specific delivery of carmustine to malignant glioblastomas for growth suppression functionalized with anti-EGFR Antibody [54].

αvβ3 integrin receptor-mediated active targeting

It consists of transmembrane glycoproteins, can mediate cell-cell and cell-extracellular matrix adhesion. More than 23 integrin heterodimers have been identified in humans. It controls the connection between the Extracellular Matrix (ECM) and the cell cytoskeleton as well as maintain communications between cells. Integrin plays a significant role in several signalling pathways involved in cell proliferation after combining with ECM. For providing precision tumour treatment strategies, nanoparticles can preferentially and effectively target integrin binding sites in tumours [55].

iii. **Folate receptor (FR) – mediated active targeting**

It is a class of glycoproteins; classified into 3 subtypes, FRα, FRβ and FRγ. FRα and FRβ can bind to the tumour cell membrane via a glycosylphosphatidylinositol anchor, while FRγ has only bind to the hematopoietic cells. FRα is widely used in various tumour cells, especially in breast, lung, kidney, cervical and ovarian cancer. FR can transport folate into tumour cells via the receptor-mediated endocytosis process [56].

iv. **Transferrin (Tf) receptor – mediated active targeting**

Tf plays an important role in Fe metabolism and delivery for maintaining cell growth and division. Tf receptors are used for the pancreas, breast, prostate, colon and lung cancer and also block normal receptor function, resulting in cell death. It shows excellent antitumor effects with few side effects [57].

v. **Human Epidermal growth factor Receptor 2 (HER2) – mediated active targeting**

HER plays an important role in the pathogenesis of various tumour including gastric and widely used for breast cancer. HER subtypes are HER1, HER2, HER3, HER4. HER-targeting-based strategies may include tumour chemoresistance as their

associated receptors, possess tyrosine kinase catalytic activity. HER2 receptors does not have a natural ligand, it can dimerize with other ErbB family receptors to activate the HER signalling pathways [58].

vi. **Estrogen receptor – mediated active targeting**

Estrogen is a steroid hormone, to maintain reproductive system function, bone homeostasis, brain development and cardiovascular remodelling. The 3 forms of this are, Estrone (E1), Estradiol (E2) and Estriol (E3). E2 is important for breast, endometrial and ovarian cancers. Function of estrogen is binding and subsequent activation of two structurally different estrogen receptors (ERα and ERβ). For enhanced tumour treatments modified nanoparticles were effectively internalized by tumour cells using the ERα receptor-mediated endocytosis process [59].

vii. **Cluster of Differentiation (CD) receptor**

Mediated active targeting. Cd receptors subtypes are cd14, cd22, cd36, cd44 and cd133, can be used as promising delivery targets against tumour metastasis. Cd44 is a transmembrane adhesion glycoprotein, used to target receptors for targeted tumour treatment. Hyaluronic acid (ha) has been widely used in cd44 receptor-mediated active targeting delivery systems [60].

viii. other receptor – mediated active targeting systems

Other receptors have been used to design targeted anti-cancer nanoplatforms, including chemokine, biotin and luteinizing hormone-releasing hormone (LHRH) receptors. These receptor-mediated strategies have shown potential advantages for drug delivery, several factors such as ligand, stability, orientation and density must be taken to preserve the function of the targeting ligand.

Stimuli-responsive targeting strategies

1) Endogenous Stimuli-responsive targeting strategies

A. Redox-responsive targeting strategies

i) Reactive Oxygen Species (ROS)-responsive targeting strategies

ii) Reactive Nitrogen Species (RNS)-responsive targeting strategies

iii) Glutathione (GSH)-responsive targeting strategies

iv) ROS and GSH dual-responsive tumour-targeting strategies

B. pH-responsive targeting strategies

i) Protonation and deprotonation-based nanoplatforms

ii) Acid-sensitive bond cleavage-based nanoparticles

C. Enzyme-responsive targeting strategies

i) Matrix Metalloproteinases (MMPs)-responsive nanoplatforms

ii) Heparinase-responsive nanoplatforms

iii) Cathepsin-sensitive nanocarriers

D. Hypoxia-responsive targeting strategies

i) Hypoxia-responsive drug delivery

ii) Azobenzene (AZO) compounds

iii) Oxide groups

iv) Quinone Compounds

v) Hypoxia-responsive O_2 release

vi) Hypoxia-mediated O_2 production

E. Interstitial Fluid Pressure (IFP)-related targeting strategies

F. ATP-responsive targeting strategies

2) Exogenous Stimuli-responsive targeting strategies

A. Temperature stimuli-responsive targeting strategies

B. Magnetic stimuli-responsive targeting strategies

C. Ultrasound stimuli-responsive targeting strategies

D. Laser stimuli-responsive targeting strategies

THE FUTURE OF NANOPARTICLES

The future of nanotechnology has been a subject of many clinical and non-scientific speculations, which include numerous doomsday visions in famous culture that predicted self-replicating nano debris taking component in massive attacks on humanity and the surroundings. NPs have varied applications in ocular drug delivery, in intravenous drug delivery, as carriers for radionucleotides, as cosmetics for skin care, as controlled release medication etc. From the fabrication perspective, conventional techniques have the advantage of easy scale up, but lose accuracy in control over particle characteristics.

CONCLUSIONS

Nanoparticles offer promising avenues in various fields due to their unique properties, but ensuring their stability and accurate evaluation are paramount. In this article, we have reviewed nanoparticle as it associates to stability issues and the evaluation aspects and we have furnished the therapeutic strategy for nanoparticles in different therapies over an extensive clinical use.

Establishing standardized protocols for stability assessment and evaluation methods is essential for advancing nanoparticle research and their practical applications. Further research should focus on addressing challenges such as long-term stability, biocompatibility, and environmental impact to unlock the full potential of nanoparticles in diverse applications. Furthermore, advancements in nanoparticle synthesis techniques and characterization methods are necessary to enhance stability and accurately evaluate their performance. Collaborative efforts between scientists, engineers, and regulators are crucial for developing comprehensive guidelines and regulations to govern the use of nanoparticles safely and effectively. By addressing these challenges and fostering interdisciplinary collaboration, nanoparticles can continue to revolutionize industries ranging from healthcare to environmental remediation.

DECLARATION

There is no conflict of interest in publishing this review article.

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