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A Review: Nanocarriers Drug Delivery System

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ABSTRACT:

Nanocarriers have recently emerged as the perfect answer for effective and secure drug release. The exceptional properties that nanoparticles display when compared to their bigger scaled equivalents are mostly to blame for this. Due to their high biocompatibility, a variety of these carriers are increasingly widely used, providing improved efficacy, particularly in cancer treatments. The ability of nanotechnology to accurately identify and cure different malignancies has recently attracted more interest. The shortcomings of conventional anticancer drug delivery systems, such as their non-specificity, severe side effects, burst release, and harm to healthy cells, have been overcome using nanocarriers. Due to their useful advantages, such as protection from degradation in a challenging physiological environment, enhancement of plasma half-life and retention time, facilitation of absorption through the epithelium, site-specific delivery, and improved access to intracellular targets, nanocarriers are crucial for the effective delivery of biopharmaceuticals. The clinical and financial success of biopharmaceuticals is highlighted in the current review, along with the broad applications and potential of nanocarriers in the delivery of biopharmaceuticals. Here, we describe practical uses of nanocarriers for the oral, pulmonary, nasal, and cutaneous delivery of biopharmaceuticals via invasive and non-invasive routes ,their types and integration of nanocarriers with Artificial Intelligence.

Keywords: Nanocarriers , Biocompatibility, Nanotechnology, Biopharmaceuticals, Artificial Intelligence.

INTRODUCTION:

Nanomaterials are substances with one or more dimensions less than 100 nm.[1] A nanomaterial is, to put it more precisely, "a natural, incidental, or manufactured material containing particles, in an unbound state, as an aggregate, or as an agglomerate, and where, for 50% or more of the particles in the number size distribution, one or more external dimensions is in the size range 1 nm-100 nm".[2]

When compared to their larger sized forms, nanomaterials have exceptional optical, electrical, and/or mechanical qualities. They may differ from macro forms in terms of colour, conductivity, reactivity, surface area to volume ratio, and surface tension. Because of this, nanomaterials have caught the interest of scientists due to their potential application in the production of vaccines, medications, and drug delivery[3]. Nanocarriers are colloidal drug delivery devices that typically have 500 nm-sized submicron particles. Over the past few decades, there has been a lot of research done on nanocarriers since they have shown great promise for medication delivery.[4] Due to their high surface area to volume ratio, nanocarriers can change the fundamental characteristics and bioactivity of medicines. Some of the properties that nanocarriers can incorporate in drug delivery systems include enhanced pharmacokinetics and biodistribution, lower toxicities, improved solubility and stability, controlled release, and site-specific delivery of therapeutic agents[5,6]. Nanotechnology has recently become a useful tool for getting beyond the limitations of traditional medicine delivery technologies. For improved pharmacokinetic and biodistribution profiles, decreased toxicity, controlled release, enhanced solubility and stability, and site-specific delivery of their payload, nanocarriers can alter the fundamental characteristics and bioactivity of their encapsulated moiety [7,8]. By modifying their composition, shape, size, and surface qualities, nanocarriers can also be produced to exhibit a wide variety of physicochemical properties [9,10]. Both organic and inorganic systems can be used as nanocarriers. Inorganic nanocarriers include mesoporous silica nanoparticles (MSNs) and metallic nanoparticles, whereas organic nanocarriers include liposomes, lipid nanoparticles, polymeric nanoparticles, dendrimers, micelles, and virus-like particles (VLPs) [11].

Aqueous phase and phospholipid and cholesterol bilayers surround an aqueous phase to form spherical vesicles known as liposomes. Depending on the composition and preparation process, they may have different physical and chemical characteristics. Due to their versatility, safety, and ease of surface modification, liposomes make good delivery vehicles for biopharmaceuticals [12,13]. Triglycerides, partial glycerides, fatty acids, waxes, and various surfactant mixtures make up lipid nanoparticles. Lipid nanoparticles exhibit effective and targeted drug delivery and typically have particle sizes < 1 m [14,15]. Biocompatible and non-toxic natural or synthetic polymers are used to create nanosized carriers in polymeric nanoparticles. They either contain matrix (nanospheres) or vesicular (nano capsules) systems [16]. Block copolymer transporters known as polymeric micelles have a core-shell structure. The structural and physical characteristics of block copolymers may be used to regulate the size, shape, and critical micelle concentration of polymeric micelles [17]. Organic nanocarriers called dendrimers have branched structures that grow out of a central core. Dendrimers have drug molecules bonded to them in the form of complexes or capsules, and surface modification is made feasible via physical and chemical links [18]. Nanogels are three-dimensional networks that are submicron in size and are created when polymers are physically or chemically crosslinked. Due to their superior drug loading capacity, high stability, biologic consistency, and stimuli-responsiveness to ionic strength, pH, and temperature, nanogels are desirable

nanocarriers. Nanogels can also swell and absorb large volumes of water or biological fluids because to their cross-linked networks. They are a promising medication delivery technique because to these distinctive qualities [19,20].

Pharmaceutical corporations are reluctant to spend more money on natural product-based drug discovery and drug delivery systems despite the benefits, preferring to search through libraries of chemical compounds instead to find new medications. Natural substances are, however, currently being tested for the treatment of a number of serious illnesses, including as cancer, diabetes, cardiovascular, inflammatory, and microbiological diseases. This is mainly due to the distinctive benefits that natural medicines provide, such as reduced toxicity and side effects, low cost, and strong therapeutic potential. However, employing natural chemicals as medication is more difficult due to worries about their biocompatibility and toxicity. Because of these issues, many natural substances are failing to get past the clinical trial phases. [21,22]. Major difficulties arise when using large-scale materials for drug administration, including in vivo instability, low bioavailability and solubility, poor body absorption, problems with target-specific distribution, and possible negative therapeutic effects. Therefore, adopting innovative drug delivery systems to direct medications into particular body areas may be an alternative to address these pressing problems [23,24]. Therefore, nanotechnology has a major impact on modern drug formulations, their controlled drug release, and delivery with great success. Nanomaterials, which affect the frontiers of nanomedicine from biosensors, microfluidics, drug delivery, and tissue engineering, can be simply characterized as materials with diameters ranging from 1 to 100 nm [25,26]. To create nanomedicines, nanotechnology uses therapeutic molecules at the nanoscale level. Nanoparticles have been the driving force behind the development of nanobiotechnology, drug delivery, biosensors, and tissue engineering in the biomedical industry. Nanoparticles are typically small nanospheres because they are made of materials that are designed at the atomic or molecular level. As a result, they can travel within the human body with greater freedom than bulkier materials. The structural, chemical, mechanical, magnetic, electrical, and biological characteristics of nanoscale-sized particles are distinctive. [27,29] When creating target-specific drug delivery systems, metallic, organic, inorganic, and polymeric nanostructures, such as dendrimers, micelles, and liposomes, are commonly taken into account. These nanoparticles are attached to medications that have limited solubility and poor absorption capacity [28, 30]. The effectiveness of these nanostructures as drug delivery systems, however, differs based on their size, shape, and additional inherent biophysical/chemical properties. For instance, polymeric nanoparticles with diameters between 10 and 1000 nm have properties that make them ideal as effective delivery systems.[22]. Numerous synthetic polymers, including polyvinyl alcohol, poly-l-lactic acid, polyethylene glycol, and poly(lactic-co-glycolic acid), as well as natural polymers, like alginate and chitosan, are widely used in the nanofabrication of nanoparticles due to their high biocompatibility and biodegradability properties. Both the nanosphere and the nanocapsule subtypes of polymeric nanoparticles are effective drug delivery devices. Similar to liposomes and micelles, compact lipid nanostructures and phospholipids are particularly helpful in the delivery of targeted drugs. The biophysical and biochemical characteristics of the targeted medications chosen for therapy are the primary factors used to determine the adoption of an optimum nanodrug delivery system. [31]

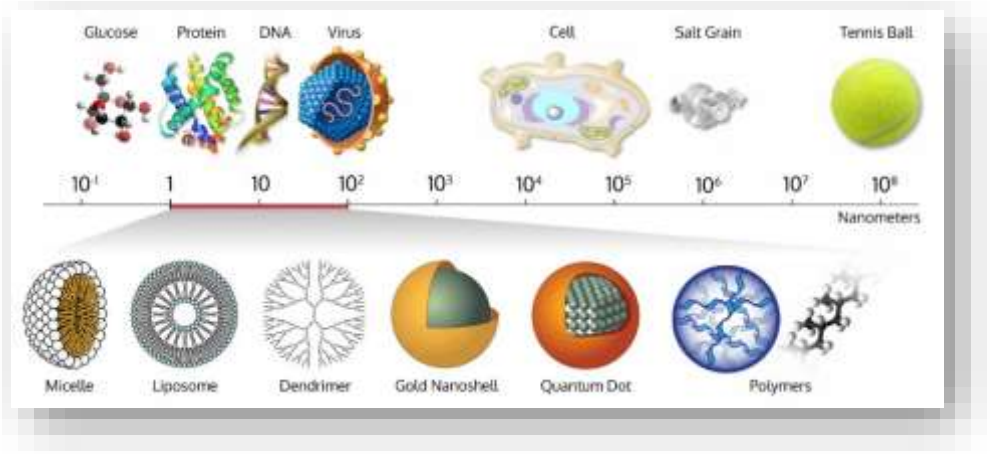

Fig 1: Nanoparticles Size

Using nanoscale materials, such as biocompatible nanoparticles and nanorobots for diverse applications, including diagnosis, delivery, sensory, or actuation functions in a living organism, nanomedicine is the discipline of medicine that makes use of the science of nanotechnology. Drugs with extremely low solubility have a variety of biopharmaceutical delivery problems, such as limited bioaccessibility following oral intake, reduced ability to diffuse into the outer membrane, need for greater intravenous dosage, and unfavourable side effects prior to conventionally formulated vaccination process. However, all of these restrictions could be removed by incorporating nanotechnology methods into the medication delivery system. [32].

A number of nanocarrier-based products have been approved for the treatment of various tumours, and many others are in different phases of clinical trials. Also there are various nanocarrier based drug delivery systems for selected tumour's. In this review we are going to discussed about types of nanocarriers ,their mechanism ,various advantages of nanotechnology and its future prospectives.

TYPES OF NANOCARRIERS USED IN DRUG DELIVERY SYSTEMS:

Organic Nanocarriers:

Solid nanoparticles of lipids (SLNs)

SLNs are nanosized colloidal drug carriers with a size range of 50–1,000 nm that were created in the early 1990s.

[33] Emulsifier(s) are utilized to stabilize the dispersion while emulsifier(s) are used to prepare SLNs by dispersing melted solid lipid(s) in water. High pressure homogenization and microemulsification are the two approaches that are most frequently utilized to create SLNs. SLNs offer a highly lipophilic lipid matrix for the dispersion or dissolution of medicines. [34] For the creation of SLNs, a wide range of solid lipids, such as mono-, di-, and triglycerides; free fatty acids; free fatty alcohols; waxes; and steroids, have been used. Except for the fact that different types of lipids are employed in both formulations, SLNs and nanoemulsions are relatively comparable. In contrast to the liquid lipids (oils) utilized in nanoemulsions, solid at room temperature lipids are used in SLNs. Over their colloidal counterparts, such as nanoemulsions, liposomes, and polymeric nanoparticles, SLNs as nanocarriers have a variety of advantages (PNPs). Controlled drug delivery, absence of biotoxicity, high drug payload, enhanced bioavailability of poorly water-soluble medicines, superior stability, and simple and affordable large-scale manufacture are some of the areas where SLNs outperform their competitors. [35] Several models for include pharmaceuticals in SLNs have been put forth. Drug can be incorporated into the lipid matrix of SLNs (solid solution/homogeneous matrix model), the shell surrounding the lipid core (drug-enriched shell model), or the core surrounded by a lipid shell, depending on the composition of SLNs (lipid, drug, and surfactant), and the production conditions (hot or cold homogenization) (drugenriched core model). [36]

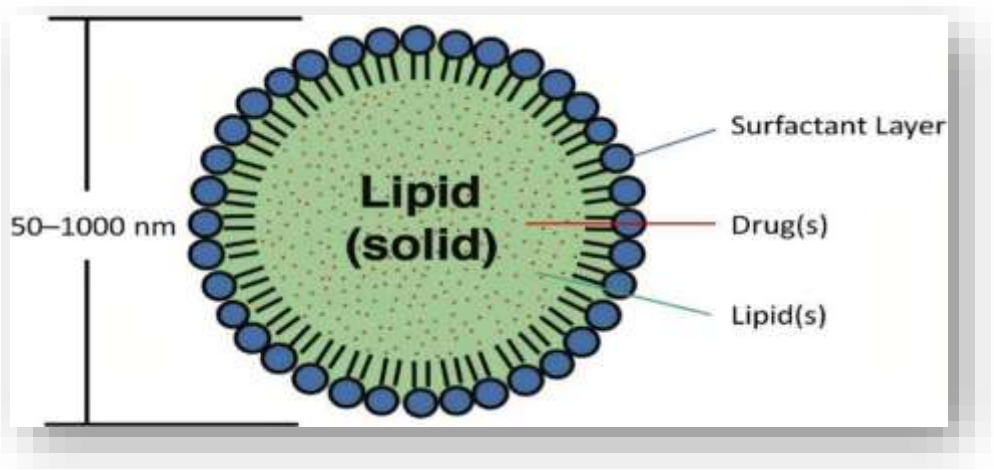

Fig 2: Solid Lipid Nanoparticle

Dendrimers:

Often branching macromolecules, dendrimers have several arms that branch out of a central core. They are often made utilizing natural or synthetic ingredients such sugars, nucleotides, and amino acids. They may modify molecules with an incredibly consistent branching pattern, a specific molecular weight, and a distinctive number of peripheral groups because to their stepwise synthesis. Because of the well-organized and irregular branching patterns, respectively, dendrimers made using stepwise synthetic procedures can be distinguished from those made using polymerization processes. [37]

According to Lai et al., dendrimers were successfully employed to increase the effectiveness of doxorubicin. They employed the photochemical internalization (PCI) technique, which is well known for removing the cytoplasmic membrane and allowing macromolecules held in cytoplasmic vesicles to be released, increasing the cytotoxicity to malignant tissue. [38] After being administered intraperitoneally to mice harboring B16F10 tumor cells, cisplatin-dendrimer conjugation was found to have increased activity both in vitro and in vivo when compared to free cisplatin. Similar to cisplatin alone, dendrimer-platinate conjugation improved anticancer activity following intravenous treatment. In a different attempt, Zhuo et al. created 5-FU-dendrimer conjugates utilizing the timesequenced propagation approach in generations ranging from 0.5 to 5.5. It was discovered that these conjugates had an advantageous controlled release property for anticancer medications. Moreover, when given subcutaneously to mice, they inhibit the growth of the Doxunresponsive C-26 tumor. In a related investigation, it was discovered that 5-FU was conjugated with PEGylated polyamidoamine (PAMAM) dendrimers, which caused a prolonged release of anticancer medicines in albino rats both in vitro and in vivo. Additionally, this trial had reduced hemolytic toxicity and leakage. [39]

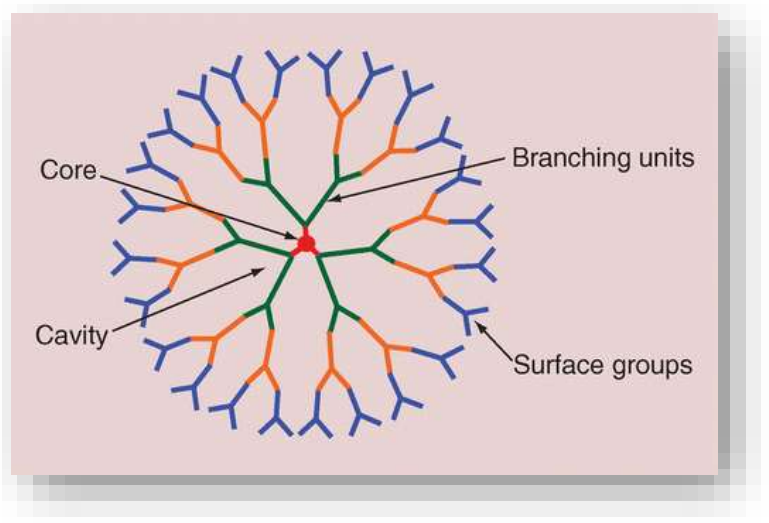

Fig 3:Dendrimers

Liposomes:

Over the past few decades, liposomes have drawn significant attention in biomedicine, particularly as a method of delivering anticancer medications. [40] They demonstrated a number of advantages over conventional systems, including improved drug delivery, protection of the active ingredient from environmental factors, enhanced product performance features, preventing early encapsulated drug degradation, cost-effective formulations of pricey medications, and effective treatment with lower systemic toxicity. [41] In addition, when compared to free pharmaceuticals in solution, the pharmacokinetic characteristics of medications coupled with liposomes are significantly altered. To demonstrate a prolonged half-life in blood circulation, they can be coated with polymers such as polyethylene glycol (PEG; PEGylated or stealth liposomes). The aqueous core of liposomes, which are spherical vesicles, is encased in lipid bilayers. Their single or multiple bilayered membrane assemblies are made of lipids that are either natural or manufactured (Figure 4). Depending on their sizes, these are classified as tiny unilamellar vesicles or large unilamellar vesicles if they possess a single bilayer membrane. Multilamellar vesicles are referred to be such if there are more than one bilayer present. Liposomes differ in terms of composition, size, surface charge, and fabrication technique. Liposomes are frequently employed as model cells or as carriers for a variety of bioactive substances, such as medications, vaccines, cosmetics, and nutraceuticals. [41]

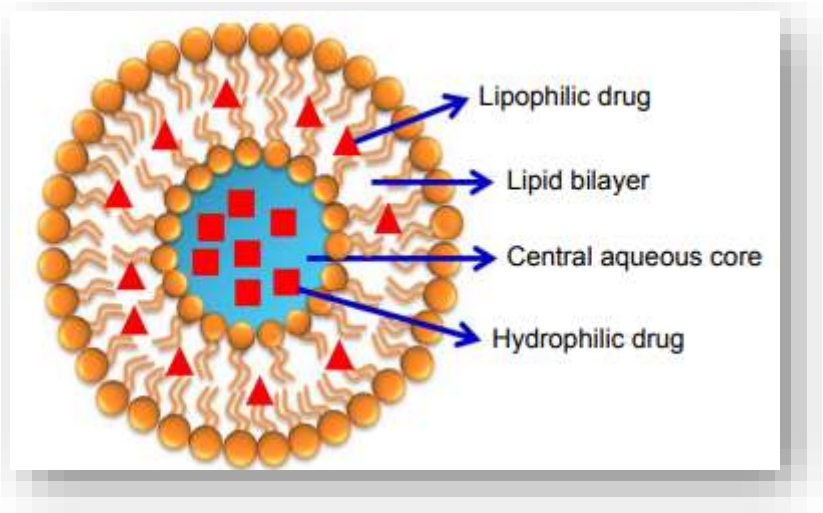

Fig 4: Diagrammatic representation of liposome structure

PNPs:

Since they provide a variety of appealing qualities in medication delivery, polymers have attracted a lot of research in the last few decades. PNPs are solid, colloidal nanoparticles (10–1,000 nm), composed of biodegradable polymers. [42] PNPs can be divided into two structural groups: nanospheres (of the matrix type) and nanocapsules (reservoir type; Figure 5). In contrast to nanocapsules, which dissolve/disperse the drug in a liquid core of oil or water

enclosed by a solid polymeric membrane, nanospheres type PNPs entrap the drug in the polymer matrix. Both PNP kinds allow for the chemical conjugation or adsorption of the medication on the surface (of the matrix or capsule). [43] Depending on the composition and required features of PNPs, various preparation techniques have been devised. These techniques can easily be divided into two groups: direct monomer polymerization and dispersion of premade polymers. Solvent evaporation, salting out, nanoprecipitation, dialysis, and supercritical fluid technology are some of the techniques used to disperse premade polymers. Emulsification polymerization, miniemulsion polymerization, microemulsion polymerization, interfacial polymerization, and controlled/living radical polymerization are some of the techniques that directly polymerize monomers. Rao and Geckeler have thoroughly examined each of these techniques. [42] PNPs have been created using a variety of biocompatible and biodegradable natural and synthetic polymers. Because they are biodegradable, these polymers are broken down into individual monomers inside the body and eliminated by regular metabolic processes. The synthetic polymers polylactic acid (PLA), polyglycolic acid (PGA), polylactic acid (PLGA), polyglycolic acid (PLGA), polycaprolactone (PCL), copolymer N-(2-hydroxypropyl)methacrylamide (HPMA), polyaspartic acid (PAA), and polyglutamic acid are the most often utilized ones. Albumin, alginate, chitosan, collagen, dextran, gelatin, and heparin are among the most frequently utilized natural polymers. Compared to their colloidal counterparts, such as polymeric micelles (PMs) and liposomes, PNPs offer better stability on storage and in vivo (in the blood), a higher drug payload, a more homogeneous particle size distribution, better and controllable physicochemical properties, higher drug circulation times, and more controlled drug release. These features are in addition to the general salient characteristics shared by all nanocarriers in cancer therapy. [44] In the context of cancer treatment, each of these qualities is extremely desirable.

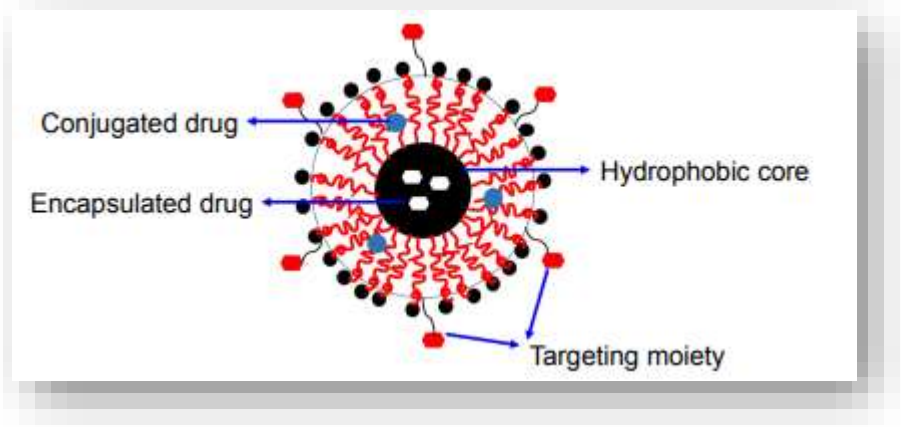

Fig 5: Schematics of PNPs

PMs:

PMs are synthetic amphiphilic di- or tri-block copolymers that self-assemble into nanosized (10–100 nm) colloidal particles in an aqueous environment. Di- or tri-block copolymers contain both hydrophobic and hydrophilic segments because they are amphiphilic in nature. Above a particular concentration (referred to as the critical micelle concentration [CMC]), these block copolymers form micelles when exposed to an aqueous environment. Block copolymer's hydrophobic segment makes up the micelle's core, while its hydrophilic segment makes up its shell. A hydrophobic core and a hydrophilic shell make up the core/shell structure of PMs (Figure 5). [45] The hydrophobic core of PMs permits hydrophobic medications to be trapped and regulates the release of pharmaceuticals from PMs. The hydrophilic shell of PMs, however, controls in vivo pharmacokinetics, ensures the solubility of the PMs in the aqueous environment, and stabilizes the core. The drugs can either be incorporated into the PMs by physical entrapment or via chemical attachment. Some frequently used methods for the preparation of PMs include the dialysis method, oil-in-water emulsion method, solvent evaporation method, co-solvent evaporation method .[46]

Inorganic nanocarriers:

Carbon nanotubes (CNTs):

CNTs are nanoscale, hollow carbon atom tube-like structures that were first identified by Iijima in 1991. CNTs are made by wrapping up graphene sheets into a tube-like shape and are a member of the family of fullerenes, which is a third allotropic form of carbon. [47] Single-walled carbon nanotubes (SWCNTs), which are produced by rolling up a single graphene sheet, and multi-walled carbon nanotubes (MWCNTs), which are produced by rolling up several concentric graphene sheets into a tubelike assembly, are two different types of CNTs (Figure 6A and B). CNTs can extend over a thousand times longer than their diameters and have cross-sectional dimensions in the nanoscale range. SWCNTs and MWCNTs typically have outside diameters between 0.4 and 2 nm and 2 and 100 nm, respectively.

CNTs are a viable medication delivery vehicle because they have unique physicochemical and biological properties. Nanoneedle shape, hollow monolithic structure, high aspect ratio (length: diameter.200:1), extremely high surface area, extremely light weight, high mechanical strength, highly elevated electrical and thermal conductivities, and the capacity for surface modification are a few of these characteristics. [48] CNTs' needle-like shape enables

them to enter the cell through "needle-like penetration" or endocytosis, which involves crossing the cell membrane. CNTs' poor water solubility and toxicity are the main drawbacks of using them as a medication delivery system. CNTs can, however, be surface functionalized, which makes them water soluble, biocompatible, non- or less poisonous, and a carrier that is stable in serum. [49]

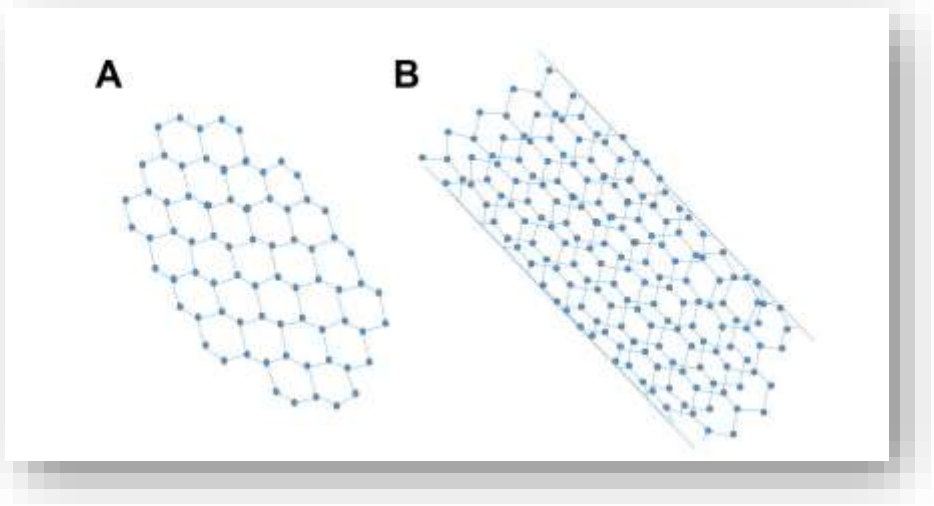

Figure 6: Graphical representation of SWCNTs (A) and double-walled CNTs (B)

Mesoporous silica nanoparticles (MSNs):

Due to their straightforward synthesis processes and capacity to be produced in large quantities, silica (SiO2) materials have seen an upsurge in applications in the field of biomedicine. Mesoporous silicas are a type of silica material that is particularly significant for drug delivery because of its ability to hold huge amounts of medication due to their honeycomb-like structure and numerous pores (Figure 7). [50] MSNs are promising nanoscale drug carriers because they have a number of desirable properties, including high loading capacity, controllable pore diameters ranging from 2 to 50 nm with narrow pore size distribution, good thermal and chemical stability, and versatility in loading drugs with hydrophilic and lipophilic properties. [50,51]

The ability of MSNs to easily surface functionalize for controlled and targeted drug delivery also allows them to improve therapeutic efficacy and lessen medication toxicity. MSNs' distinctive construction and appealing qualities put this class of nanocarriers in a prime position for the delivery of anticancer medications. Large amounts of anticancer drugs can be loaded into MSNs due to their mesoporous structure, which also helps them accumulate in tumor tissues through passive targeting. Additionally, MSNs' convenient surface functionalization with various site-specific targeting agents allows them to actively target tumor tissues. [52] MSNs have been successfully used to administer a variety of anticancer medications, including paclitaxel, camptothecin, doxorubicin, and methotrexate.

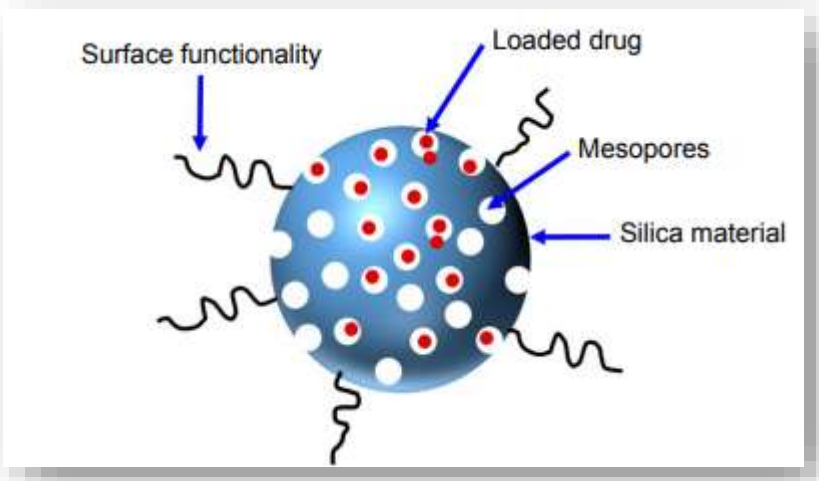

Fig 7: Schematics of MSNs.

Organic/inorganic hybrid nanocarriers:

To combine the benefits of organic and inorganic materials, organic/inorganic hybrid nanocarriers have been produced. To improve the selectivity and effectiveness of anticancer medicines, certain functionalities of organic components at the surface of inorganic NPs have been used. For instance, treating surfaces with polyethyleneimine (PEI) results in cationic surfaces that may carry nucleic acids effectively while also improving cellular uptake of MSNs. 84 Another study found that the integration of hyperbranched PEI with MSNs produced prolonged intracellular delivery of short interfering RNA with a high payload (siRNA). [53] These hybrid MSN/PEI nanocarriers were able to enter the tumor microenvironment and then leak from endosomes into the cytoplasm. Due to its potential use in nanotechnology and biomaterials, systems made of lipid bilayers supported on solid material have drawn a great deal of attention. One of these systems is the MSNs/lipid bilayer hybrid nanocarrier, which uses lipid bilayers to plug the channels of MSNs in order to delay the release of hydrophilic drug cargo, overcome multidrug resistance, and enable stimuli-responsive drug release. [54] In order to increase the retention and intracellular delivery of zoledronic acid in breast cancer, Desai et al. announced the development of a hybrid MSNs/lipid bilayer system. Han et al. created doxorubicin-loaded, hybrid, lipid-capped MSNs with pH and redox-responsive drug cargo release in a different study. In comparison to the free drug solution, these hybrid nanocarriers demonstrated improved doxorubicin absorption efficiency, cytotoxicity, and intracellular accumulation. They also were able to release doxorubicin within the tumor cells. [55]

Drug designing and drug delivery process and mechanism:

In order to improve the drug specificity and diagnostic accuracy, different therapeutic procedures have been presented and conventional clinical diagnostic approaches have been investigated. These developments are related to the development of nanomedicine, drug discovery/design, and drug delivery systems. For instance, new medication delivery methods are being investigated, with a focus on ensuring that they have a focused effect in particular places, which lowers their toxicity and increases their bioavailability in the organism [56].

Drug designing has been a promising aspect of the identification of novel lead medications based on the understanding of a biological target in this context. The expansion and improvement of this industry depend on the development of experimental techniques for the classification and purification of proteins, peptides, and biological targets as well as advances in computer sciences. [57] Additionally, there are a number of studies and reviews in this field that emphasize the rational design of various compounds and highlight the significance of researching various drug release mechanisms. Additionally, natural products can inspire the creation of new drugs with desired physicochemical features and offer workable and intriguing solutions to the problems associated with drug design .[58, 59]

Additionally, over the past few years, the importance of medication delivery systems has increased. These systems are simple to create and have the potential to encourage the modified release of the active components in the body. For instance, Chen et al. presented the therapeutic effects of their intriguing research using nanocarriers for imaging and sensory applications. Additionally, Pelaz et al. [60] explored fresh prospects and difficulties for this industry while providing an up-to-date summary of many nanocarrier applications to nanomedicine. It's interesting to note that each of these drug delivery methods has distinct chemical, physical, and morphological properties and may be compatible with various drug polarities through chemical or physical interactions (such as covalent bonds and hydrogen bonds) (e.g., electrostatic and van der Waals interactions). For instance, Mattos et al. [61] showed that the release profle of biogenic silica nanoparticles grafted with neem bark extract (chemical interactions) was lower than that of biogenic silica nanoparticles loaded with neem bark extract. Therefore, all of these variables affect how nanocarriers interact with biological systems as well as how quickly the active ingredient is released inside of an organism [62]. Additionally, Sethi et al created a crosslinkable lipid shell (CLS) that contained the prototype medicines docetaxel and wortmannin for regulating drug discharge kinetics. After studying the CLS's discharge profle, they discovered that it was affected in both in vivo and in vitro settings. Other factors, such as the nanocarriers' composition (for example, organic, inorganic, and hybrid materials) and the way that pharmaceuticals are attached to them (for example, a core-shell system or matrix system), are also essential for comprehending its drug delivery profile. [63]

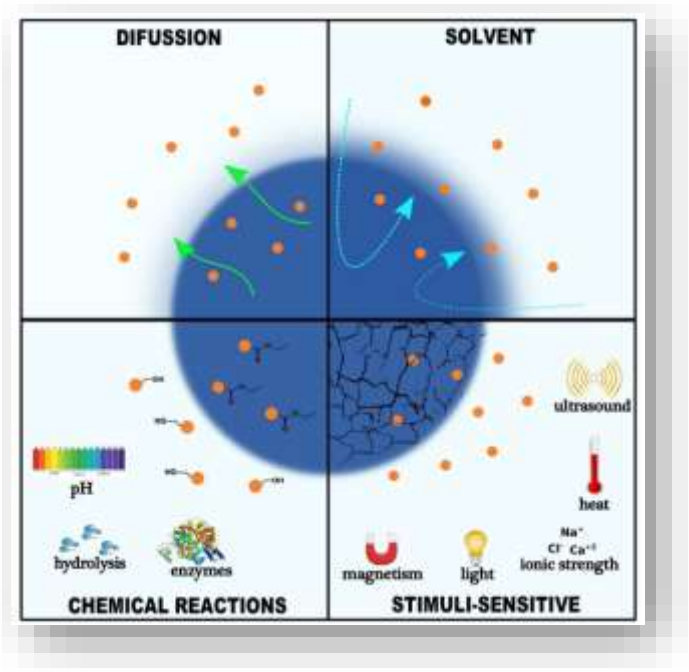

Fig 8: Mechanisms for controlled release of drugs using diferent types of nanocarriers

Active mechanism:

Surface modification of nanocarriers with site-specific targeting ligands allows for active targeting of specific tumor tissues (Figure 9B). The targeting ligands can bind to particular receptors that are only overexpressed by tumor cells or the vasculature of tumors. [64] Small molecules, antibodies and antibody fragments, peptides such arginylglycylaspartic acid (RGD), glycoproteins like transferrin, vitamins like folic acid, growth hormones, and nucleic acids are among the targeting agents frequently utilized to improve the site specificity of nanocarriers. Nanocarriers with a high surface area to volume ratio can bind several targeting moieties efficiently, improving the targeting of particular tumor cell types. [65] In addition to reducing the off-target delivery of chemotherapy drugs, active tumor targeting also helps patients avoid the limitations of passive tumor targeting and overcome multiple drug resistance.[66] The chosen targeting moiety must exclusively bind to a receptor that is overexpressed by tumor cells solely for the active targeting technique to be effective. The desired target receptor must also be uniformly expressed in all target cells. [67]

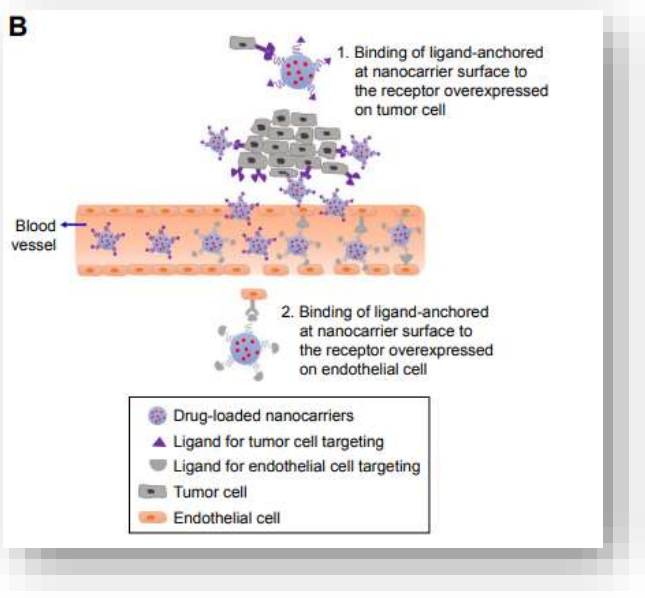

Fig 9:Active mechanism targeted on tumour

Selected tumors and relative nanocarriers:

In all cases, tumors are primarily brought on by mutations or other defects in the tumor suppressor genes, which prevent cell growth and promote programmed cell death, or in the proto-oncogenes, which regulate cell proliferation and differentiation (apoptosis). The development of malignant cells with their distinct characteristics of unchecked cell growth, inability to stop excessive cell division, lack of apoptosis, and capacity to penetrate nearby and distant tissues is caused by these altered genes. [68] Radiation, chemical agents, such as carcinogens, physical irritants, hereditary factors, and viruses are risk factors for genetic alterations. With a rate of 10 million new cases per year, tumors are one of the most deadly diseases in the world. According to a report on UK cancer research, the lifetime risk of developing cancer was 25% in 1975, rose to 45% in 2009, and is expected to reach 50% by 2027. The mortality rate of cancer has, however, decreased in recent years as a result of advances in tumor biology knowledge and in diagnostic and therapeutic methods. [69]

The harmful side effects of conventional chemotherapy used to treat tumors include toxicities to the liver, kidneys, bone marrow, lungs, gastrointestinal tract, and heart.By specifically targeting the tumor cells while sparing the normal cells from the damaging effects of the medicine, researchers are attempting to reduce the dosage of chemotherapeutic drugs. The creation of nanocarriers, which show significant potential for improving the therapeutic potency and safety profile of conventional chemotherapeutic drugs, is one of this field's turning points. These drug-loaded nanocarriers can either use the pathophysiology of tumors to their advantage or can be decorated with site-specific ligands to deliver antitumor chemotherapeutics to the tumor locations. Due to their widespread incidence and high death rates, four unique tumor types—breast, pancreatic, colorectal, and lung tumors—have been chosen and detailed in this review. The applications of relative nanocarriers in these malignancies have also been reviewed (Table 1). [70]

Table 1 Antitumor drug-loaded nanocarriers for the treatment of various tumors

Nanocarrier	Drug(s)	Tumor	Benefits
SLNs	5-FU, doxorubicin, paclitaxel, methotrexate	Colon, breast, lungs, pancreatic	a) SLN formulations have been successfully prepared using a simple double emulsion procedure that offers a better flexibility and least process-related stress on the encapsulated drug. These formulae represent a platform for the preparation of SLNs for water-soluble anticancer drugs, including peptides b) They have shown higher cytotoxicity than the equivalent amount of free-drug treatment as a result of the synergetic effect
Liposomes	Doxorubicin, cisplatin, Doxil	Breast, lungs, colon	a) The therapeutic advantages of targeted liposomes compared with their nontargeting counterparts in cancer cells have been demonstrated b) Enhanced drug entrapment, leading to substantial anticancer efficacy and abridged cardiotoxicity
Dendrimers	Methotrexate, 5-FU, cisplatin, doxorubicin	Breast, skin, lungs	a) Internalization of the drug conjugates into the tumor cells, resulting in increased antitumor activity and reduced toxicity b) These conjugates were found to have favorable controlled release characteristic for anticancer drugs
PNPs	Doxorubicin, docetaxel, paclitaxel, cisplatin, imatinib mesylate	Breast, chronic myeloid leukemia	a) A single intravenous injection of doxorubicin conjugated to PLGA NP exhibited tumor suppression comparable to that by daily injection of free doxorubicin over 12 days; thus, the NP formulation was much more potent and longer lasting than conventional free doxorubicin b) Much greater cytotoxic potency to cancer cells than Taxotere (current clinical form of docetaxel) c) Paclitaxel-loaded PEG-PLGA-based NPs exhibited enhanced in vitro and in vivo cytotoxic effects compared with the commercial formulation of paclitaxel (Taxol) d) Cisplatin-loaded glycol chitosan NPs showed sustained cisplatin release, improved antitumor efficacy and decreased toxicity as compared to free drug
PMs	Methotrexate, cisplatin, paclitaxel, docetaxel, doxorubicin	Breast, skin, lungs	a) PMs increase the anticancer drug circulation time in the blood b) The smaller size (10–100 nm) and prolonged circulation times in vivo cause the PMs to preferentially accumulate in the tumor site and increase their cytotoxic effect
CNTs	Methotrexate, cisplatin, paclitaxel, doxorubicin, tripiscian, carboplatin, mitomycin C	Lungs, breast, skin	a) The needle-like shape of CNTs allows them to cross the cell membrane via endocytosis or "needle-like penetration" and subsequently enter into the cell b) They offer unique physicochemical characteristics, great drug entrapment, intrinsic stability, mechanical flexibility and suitable surface functionalization
VNPs	Doxorubicin, paclitaxel, methotrexate	Breast, colon, lungs	a) VNPs show numerous striking characters comprising biocompatibility, morphological consistency, easy surface functionalization and availability in a variety of sizes and shapes b) PEGylating the surface of VNPs can increase their circulation time in the host

Breast tumor:

The most frequently diagnosed tumor and the one that kills the most women worldwide is a breast tumor. According to the GLOBOCAN report, 522,000 deaths and 1.7 million new cases of breast tumors occurred globally in 2012. Approximately 13% of individuals experience locoregional recurrence within 9 years of primary treatment, with 25% of these patients having distant metastatic syndrome at the time of recurrence, despite the fact that contemporary treatments typically provide great immediate prognoses. [71] Additionally,.60% of people with localized breast cancer also have distant, advanced-stage cancer. The recommended course of treatment for these patients includes neoadjuvant chemotherapy, which is followed by surgical resection, radiation therapy, and subsequent adjuvant chemotherapy. One of the many aims of the neoadjuvant chemotherapy is to reduce locoregional tumor weight and size to reduce surgical process, permitting breast protection in various cases. Furthermore, neoadjuvant treatment can prevent additional metastatic spread of the disease.[72]

Pancreatic tumor:

With an estimated 53,670 newly diagnosed pancreatic tumor cases and 43,090 fatalities in the US in 2017, pancreatic tumor is thought to be the fourth most common cause of cancer mortality in both sexes. Only 10% of patients with pancreatic tumors who were discovered in time would be surgically cured. Aggressive metastatic revival, which encourages resistance to traditional chemotherapy and radiation therapy, can happen in some cases of surgically treatable tumors. Cancer diagnosis remained deprived with a survival rate of 5% every five years, despite the fact that cancer detection, surgical removal, chemotherapy, and radiation therapy had all seen major improvements. The detection of disease at advanced stages of localized tumor or metastatic tumor growth is the main reason of poor care. In contrast to those with a metastatic form of the disease, patients with advanced stage localized pancreatic tumors had a median survival of only 3-6 months. [73]

Colorectal tumor:

The third most often diagnosed tumor in men, colorectal cancer, caused 1.4 million new cases and 693,900 fatalities globally in 2012. Environmental and geographic variables are both risk factors for colon cancer. Geographical location among different nations of the world causes the colorectal tumor, while environmental influences are likely to alter the genetic mutation. The two most prevalent histological kinds of colon cancer are hyperplastic and adenomatous polyps, which are caused by mucosal colonic polyps. In hyperplastic polyps, the amount of glandular cells is increased while the amount of cytoplasmic mucus is decreased. Nuclear atypia and hyperchromatism are absent. Similar to this, adenomatous polyps are frequently palisade-shaped, hyperchromatic, cigar-shaped, and inflated. A review of the literature demonstrates that all malignancies are caused by adenomas based on their clinical, pathological, histological, and epidemiological manifestations. If a patient has a greater number of adenomas or polyps, a colon tumor may develop. If the adenomatous polyps are familial and a colectomy is not performed, the case becomes even more serious. To prevent intestinal obstruction and bleeding, colorectal patients may have resection even if distant metastases are present. This is followed by systemic chemotherapy for the treatment of metastases. For patients with symptomatic illness, several institutions favor systemic chemotherapy as the initial treatment and resection as the second. This can be due to the surgical problems, which might lead to chemotherapy being stopped. [74]

Lung tumour:

With 1.8 million new cases and 1.5 million deaths from cancer worldwide in 2012, lung tumors were predicted to be the most often found tumor and the main cause of cancer mortality in men. The majority of tumor fatalities result from the spread of lung tumor cells to secondary sites like the breast or vice versa, which is a significant obstacle to effective cancer treatment. The insufficient efficiency and specificity of current chemotherapy for lung tumors is one of its major issues. Therefore, to achieve appropriate efficacy and minimized adverse effects, it is always necessary to develop site-specific and targeted medicines. The recent advancement in nanomedicine technology has attracted a great attention as the antitumor medicine of next generation based on integrated imaging and therapeutic responses (eg, image-visible nanotherapeutics).[75]

Integration of Artificial Intelligence (AI) with Nanotechnology:

AI in Pharmaceutics and Drug Delivery:

Due to the prolonged time, increased expense, and decreased productivity of modern molecular commodities, pharmaceutics and drug delivery have recently become more and more significant in the pharmaceutical sector. However, even the development of current formulations relies on time-consuming, expensive, and unreliable classic trial and error studies. A new system known as "computational pharmaceutics" is integrating big data, AI, and multiscale modeling approaches into pharmaceutics, proposing a significant potential change to the drug delivery paradigm. This is due to the exponential growth of computing power and algorithms over the past decade. Currently, various efforts are being made to apply AI methodologies to the development of pharmaceutical products, including the prediction of activity, in vitro drug release, physical stability, in vivo pharmacokinetic parameters, drug distribution, and in vivo-in vitro correlation [76].

Fig 10:AI

In 2019, Run Han and colleagues used machine learning techniques to forecast the solid dispersion's physical stability at 3 and 6 months. Hanlu Gao and colleagues also used machine learning in 2021 to explore how solid dispersion behaves when it dissolves. With an accuracy of 85%, sensitivity of 86%, and specificity of 85% in 5-fold cross-validation, a random forest method was used to create a classification model to discriminate between two types of dissolution profiles, "spring-and-parachute" and "maintain supersaturation". With a mean absolute error of 7.78 in 5-fold cross-validation, the random forest technique was used to develop a regression model to predict the time-dependent total drug release [76].

Applications of AI in the Development and Optimization of Nanocarriers:

The ability of medication delivery to target many bodily receptors, thereby decreasing the performance of a certain function, is one present problem. Because they can be functionalized to target disease-specific cells, nanocarriers have been proven to be advantageous for directing medications to particular cells or tissues and preventing toxicity from being triggered in healthy cells. [77] The size, shape, chemical composition, and surface characteristics of nanocarriers all play a role in how well they carry drugs. Making the ideal nanocarrier DDS is difficult, though. AI and computational methods to assess drug loading, drug retention, and formulation stability can help with the optimization of the nanocarrier-drug compatibility. [77] The nanotechnology field is experiencing drastic differences in the technique and efficiency of experiments. A large number of laboratories currently use automated systems; however, the scaling-up of nanocarriers and AI-based databases has excellent promise in translation. The objective of integrating automation and AI proposes the chance to enhance targeted therapeutic nanocarriers for specific cell types and patients.[78]

AI Problems in the Development and Optimization of Nanocarriers and Pharmaceuticals:

The logical design and optimization of nanocarriers and medications have been greatly aided by the current advancements in AI technologies. The effective use of a variety of AI methodologies has reduced development time, ensured product quality, and supported productive pharmaceutical research and development. Data loss is a well-known issue when implementing machine learning algorithms, though. Since large pharmaceutical businesses typically tightly retain their records and data, this difficulty is caused by the high cost of pharmaceutical trials and the lengthy research, preparation, and optimization times. Additionally, users who want to understand how machine learning models work but are satisfied with their performance are no longer able to do so. Interpretable machine learning techniques can give more thorough insights into how pharmaceutical formulations are created. Future pharmaceutical research and development prospects will increase as the pharmaceutical business and AI methodologies become more integrated. [76] Additionally, the 3D atom currently lacks a repository for nanocarriers, which may give researchers the chance to conjugate nanocarriers with different functional groups. A collection of this kind would make it simple for researchers to decide which scaffold is best for molecular simulations. More researchers that are interested in handling and interpreting data are also urgently needed.[79]

Future of nanomedicine and drug delivery system:

One of the most exciting fields of research nowadays is nanomedicine. The results of extensive research in this field over the past 20 years have already resulted in the filing of 1500 patents and the conclusion of numerous clinical trials .[80] As mentioned in the various sections above, cancer seems to be the finest illustration of an illness that has benefited from non-medical technologies for both diagnosis and treatment. By using various types of nanoparticles for the delivery of the accurate amount of drug to the afected cells such as the cancer/tumour cells, without disturbing the physiology of the normal cells, the application of nanomedicine and nano-drug delivery system is certainly the trend that will remain to be the future arena of research and development for decades to come.

Examples of nanoparticles are included in this message, however their sizes vary, with some really measuring in nanometers and others in sub-micrometers (over 100 nm). The next area of research would be greater study of materials with more uniform uniformity and drug loading and release capacity. This review also touches on significant advancements in the usage of metals-based nanoparticles for diagnostic applications. A future expansion of the use of nanomedicines may result from the application of these metals, such as gold and silver, in both diagnostic and treatment. Gold nanoparticles, which appear to be well absorbed in soft tumor tissues and make the tumor vulnerable to radiation-based heat therapy (e.g., in the near infrared area), are one important source of interest in this direction.

Although nanomedicine and nano-drug delivery systems are widely understood, their actual impact on the healthcare system—including in the treatment and diagnosis of cancer—remains quite restricted. This is due to the fact that the sector is still relatively unexplored and has just undergone two decades of serious study. Many important, fundamental characteristics are also yet unknown. One major area for future research is the fundamental indicators of pathological tissues, such as important biological markers that enable absolute targeting without impairing normal cellular function. In the end, the use of nanomedicine will develop along with our growing understanding of diseases at the molecular level for novel diagnoses and treatments. Therefore, developing nanomedicine applications in the future will require an understanding of the molecular fingerprints of disease. Additional research would be essential for the wider application of nanomedicine beyond what we have described in this review using the well-known nanoprobes and nanotheragnostics products.

Theoretical mathematical models of prediction, technology for the assessment of these events, pharmacological effect in tissues/cellular level, and the concept of controlled release of specific medications at the troubled spots have not yet been perfected. Numerous studies in the field of nanomedicine are focused on formulation and biomaterial investigations, which seem to be the early phases of biomedicine applications. Animal studies and transdisciplinary research, which takes a significant amount of time and research resources, may yield valuable data that may be used in pharmacological therapeutic and diagnosis studies. The search for more accurate treatments and diagnoses is an increasing global trend, and the future of nanomedicine and nano-drug delivery technology appears to be promising.

The creation of nanorobots (and nanodevices) that work in tissue diagnosis and repair mechanisms with full external control mechanisms has generated a lot of attention. This is still a futuristic research that has not yet become a reality but which humanity may achieve in the very near future. But just as with their advantages, more research is needed to determine whether nanomedicines pose any risks to humans or the environment at large. Therefore, a thorough examination of the potential acute or long-term harmful effects of novel nanomaterials on people and the environment is required. As nanomedicines gain popularity, their afordability would be another area of research that needs more research input. Finally, the regulation of nanomedicines, as elaborated in the previous section will continue to evolve alongside theadvances in nanomedicine applications.[80]

Conclusion:

The recent developments in nanomedicines—including technological advancements in drug delivery for both traditional and novel medications as well as unique diagnostic approaches—are covered in the current review. A variety of nano-dimensional materials, including nanorobots and nanosensors, have been described. These materials can be used for diagnosis, precise delivery to targets, sensing, or activating chemicals in real-world systems. Nanotechnology was first primarily used to improve the solubility, absorption, bioavailability, and controlled-release of medications. Enhancing the effectiveness of known naturally occurring bioactive compounds through the use of nanotechnology has now become a common practice, despite the fact that the discovery of nanodrugs is fraught with uncertainty and the search for pharmacologically active compounds from natural sources is less popular than it was fifty years ago. The medicinal use of berberine, curcumin, ellagic acid, resveratrol, curcumin, and quercetin are some good examples. The use of nanocarriers formulated with solid lipid nanoparticles, crystal nanoparticles, liposomes, micelles, superparamagnetic iron oxide nanoparticles, and dendrimers along with gold, silver, cadmium sulphide, and titanium dioxide polymeric nanoparticles has significantly increased the efficacy of these natural products.

Novel natural biomaterials have remained in demand because to their biodegradability, biocompatibility, availability, renewable nature, and low toxicity. Beyond just identifying these polysaccharides and proteins as natural biopolymers, one of the most cutting-edge study areas nowadays is on increasing their stability in the presence of biological matrix and industrial processing conditions. There have also been numerous introductions of polymeric nanoparticles (nanocapsules and nanospheres) made using solvent evaporation, emulsion polymerization, and surfactant-free emulsion polymerization. The integration of therapy and diagnosis (theranostic), using cancer as a disease model, has garnered a lot of interest in the development of nanomedicine in recent years. Good examples include the use of oleic acid-coated iron oxide nanoparticles for near-infrared diagnostic applications, alginate and folic acid-based chitosan nanoparticles for colorectal cancer photodynamic detection, cathepsin B as a metastatic processes fuorogenic peptide probe conjugated to glycol chitosan nanoparticles, iron oxide coated hyaluronic acid as a biopolymeric material in cancer.

Since the 1990s, the number of clinical trials and products based on nanotechnology that have received FDA approval has skyrocketed. These products include synthetic polymer particles, liposome formulations, micellar nanoparticles, protein nanoparticles, nanocrystals, and many others, frequently used in conjunction with pharmaceuticals or biologics. Even though safety/toxicity evaluations and regulatory mechanisms for nanomedicines will be the focus of future research, nanomedicine has already completely changed how we find and use pharmaceuticals in biological systems. Thanks to developments in nanomedicine, we are now able to diagnose diseases and even combine diagnostic with treatment.

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