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A Scientific Overview On Nanoparticle Mediated Drug Delivery System In Cancer Therapy

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ABSTRACT

Drug delivery systems based on nanoparticles (DDS) are thought to have promise in the treatment of cancer. The nanoparticle-based DDS exhibits more efficacy than standard DDS in three ways: 1) prolonging the half-life of proteins and medications that are susceptible, 2) enhancing the solubility *of hydrophobic pharmaceuticals, and 3) permitting targeted and controlled drug release in sick sites.* The primary focus of this review is on DDS based on nanoparticles made of poly (lactic-co-glycolic acid), silica, and chitosan. Their production processes and uses in the therapy of cancer are presented. There is discussion of the present drawbacks and potential applications of nanoparticle-based DDS.

Keywords;

Drug delivery system, Nanoparticle,Controlled release,Chitosan nanoparticles,Targeted delivery,Cancer treatment .

INTRODUCTION

Drug delivery systems (DDS) have been employed to administer therapeutic compounds for the treatment of diseases both preclinically and clinically [1]. Traditional DDS is administered by injection or oral ingestion. The traditional DDS offers numerous benefits, including widespread patient acceptance and ease of administration, but it also has significant drawbacks. Limited efficacy When taken orally, many medications have varying rates of absorption. Additionally, some medications may be broken down by digestive enzymes and a low pH environment before they reach the bloodstream. Lack of selectivity: Because oral drug delivery has a poor biodistribution, it is not the best option for medications that must target particular organs. The liver or kidney, which are detoxifying organs, may absorb drugs at a rapid rate and cause Lack of selectivity: Because oral drug delivery has a poor biodistribution, it is not the best option for medications that must target particular organs. Drug absorption in the kidney or liver, which are detoxifying organs, may be high and may cause toxicity to those organs. Many of the problems can be solved by controlled drug delivery systems. Many of the drawbacks of traditional medication delivery systems can be addressed by controlled drug delivery systems. Chemotherapeutic drugs, for example, are typically administered non-specifically, damaging both cancerous and healthy cells, leading to low efficacy

and severe toxicities [2]. Chemotherapeutic chemicals would be well-transported by controlled DDSs, which would direct the drugs to the tumor site, boosting drug concentrations in cancer cells and preventing damage in healthy cells [3,4]. Furthermore, proteins and novel therapeutic agents like gene therapy and RNA interference can be delivered with the help of controlled DDSs, which shield the medications from deterioration and elimination. They can support DNA and : They can aid DNA and siRNA in avoiding enzymatic breakdown and absorption by reticuloendothelial or other tissues [5]. Since nanotechnology has advanced, nanoparticles have emerged as a viable option for regulated medication delivery systems. Particles with a diameter of roughly 10–1000 nm are frequently referred to as nanoparticles. By extending the drug's half-life, making certain hydrophobic drugs more soluble, and releasing the medication in a controlled or sustained manner, nanoparticles can increase the drug's effectiveness when used as a DDS. Additionally, stimuli-responsive nanoparticles can aid in reducing toxicity and managing the medications' biodistribution. In the 1960s, liposomes—the first DDS nanoparticles—were employed as medication and protein carriers [6]. Ever since, a growing number of materials are being turned into nanoparticles and utilized as DDSs (Fig. 1). The FDA has approved 51 nanoparticles and 77 items are undergoing clinical testing, according to a 2016 assessment by Bobo et al. [7]. Polymeric and liposomal materials make up a significant fraction of all the authorized materials for nanoparticles. Nonetheless, scientists think that more sophisticated substances like micelles, metals, and proteins can also be employed as DDSs for nanoparticles. A new phase of cancer treatment has been made possible by nanotechnology in medicine,and further study into the intersection of these two areas is warranted.In these review describes the fundamentals of using the nano-carrier system in cancer therapy

NPs IN CANCER THERAPY

Because these three factors significantly affect the effectiveness of nano-drug delivery and, consequently, regulate therapeutic efficacy, NPs used in medical treatment typically have particular sizes, shapes, and surface properties (Bahrami et al., 2017). Because they can efficiently deliver medications and produce an enhanced permeability and retention (EPR) effect, nanoparticles (NPs) with a diameter ranging from 10 to 100 nm are typically thought to be appropriate for cancer therapy. Smaller particles can easily leak from the normal vasculature (less than 1–2 nm) to damage normal cells and can be easily filtered by kidneys (less than 10 nm in diameter) (Venturoli and Rippe, 2005), while particles that are larger than 100 nm are likely to be cleared from circulation by phagocytes (Decuzzi et al., 2009) furthermore, the bioavailability and half-life of NPs can be influenced by their surface properties. For example, NPs coated with hydrophilic substances like polyethylene glycol (PEG) reduce opsonization and evade immune system clearance (Yang et al., 2014). In order to extend the time that medications are in circulation and improve their penetration and accumulation in tumors, NPs are typically altered to become hydrophilic (Perrault et al., 2009; Wong et al., 2011; Yang et al., 2014). The many properties of NPs work together to determine their therapeutic impact in the treatment of cancer. Various kinds of NPs for cancer therapy are shown in fig .

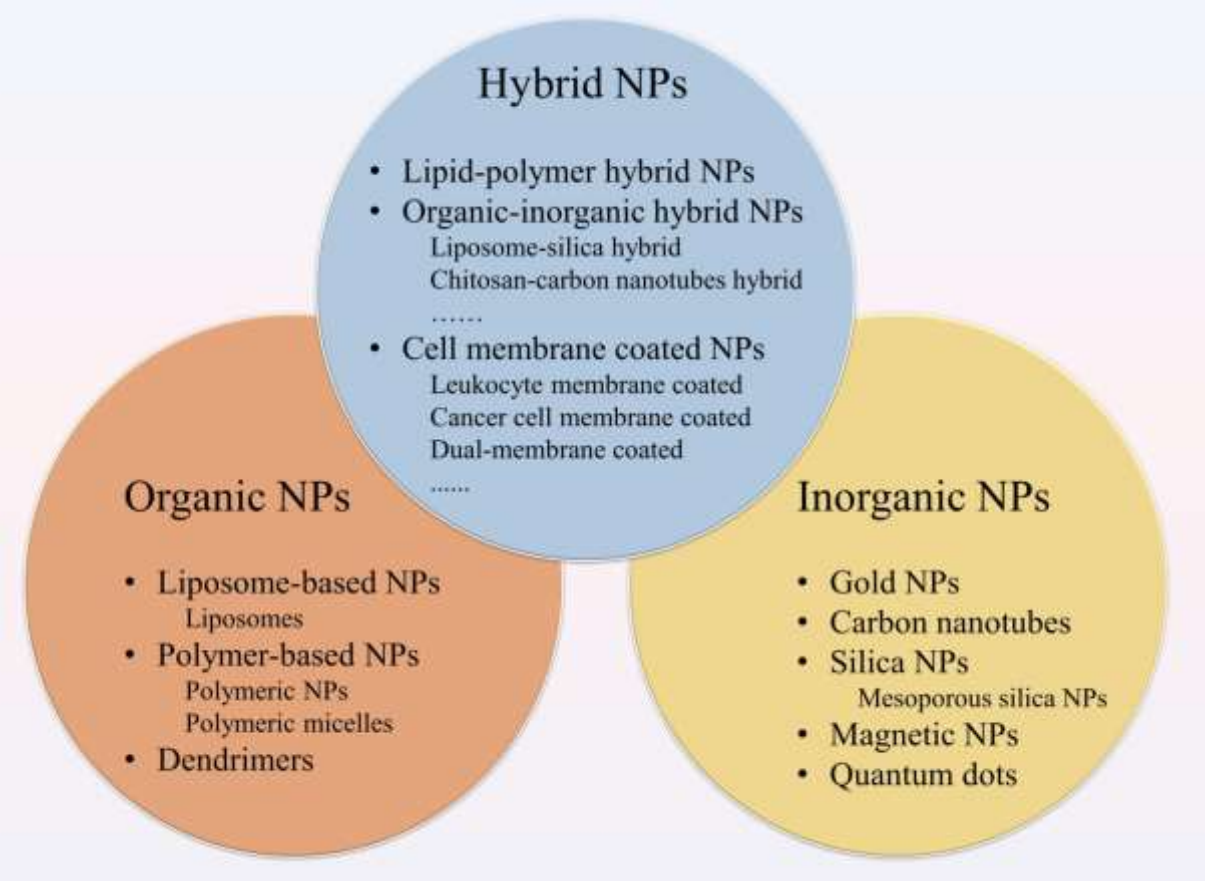

Fig.1 Different types of nanoparticles in cancer therapy[27]

This review will concentrate on three distinct kinds of DDS nanoparticles, which correspond to three distinct sources of materials used in their creation: silica nanoparticles, which are made from inorganic materials; polylactide-co-glycolic acid (PLGA) nanoparticles, which are made from synthetic polymeric material; and chitosan nanoparticles, which are a class of nanoparticles made from natural polymeric material. We will present their manufacturing processes and uses in medication delivery for the treatment of cancer.

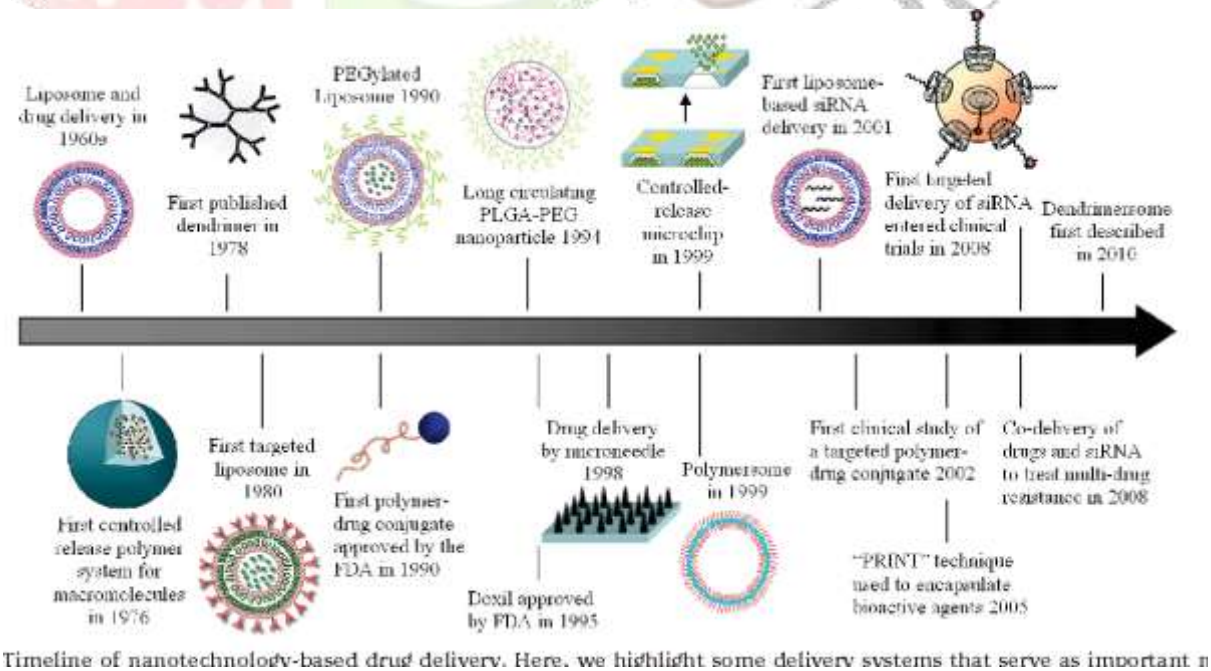

Fig.2 .Timeline for the development of nanoparticle drug delivery systems .[28]

2.Chitosan nanoparticles

Nanoparticles of chitosan The primary component of crab, lobster, and shrimp shells, chitin, is deacetylated to produce chitosan, a naturally occurring carbohydrate polymer. Chitosan is thought to be appropriate for use in pharmaceutical applications because of its low cost, good biocompatibility, minimal toxicity, and chitinase-mediated degradation in the body. Since chitosan is soluble in acidic aqueous solutions at room temperature and doesn't require heat or hazardous organic solvents, the process of creating nanoparticles from it is frequently carried out in moderate environments. Chitosan DDS can include a wide range of medications, including as proteins, polynucleotides, and tiny compounds [8]. The encapsulated medication can be released in a regulated manner via chitosan. Additionally,

The free amine groups on chitosan offer ionic crosslinking ability [9].

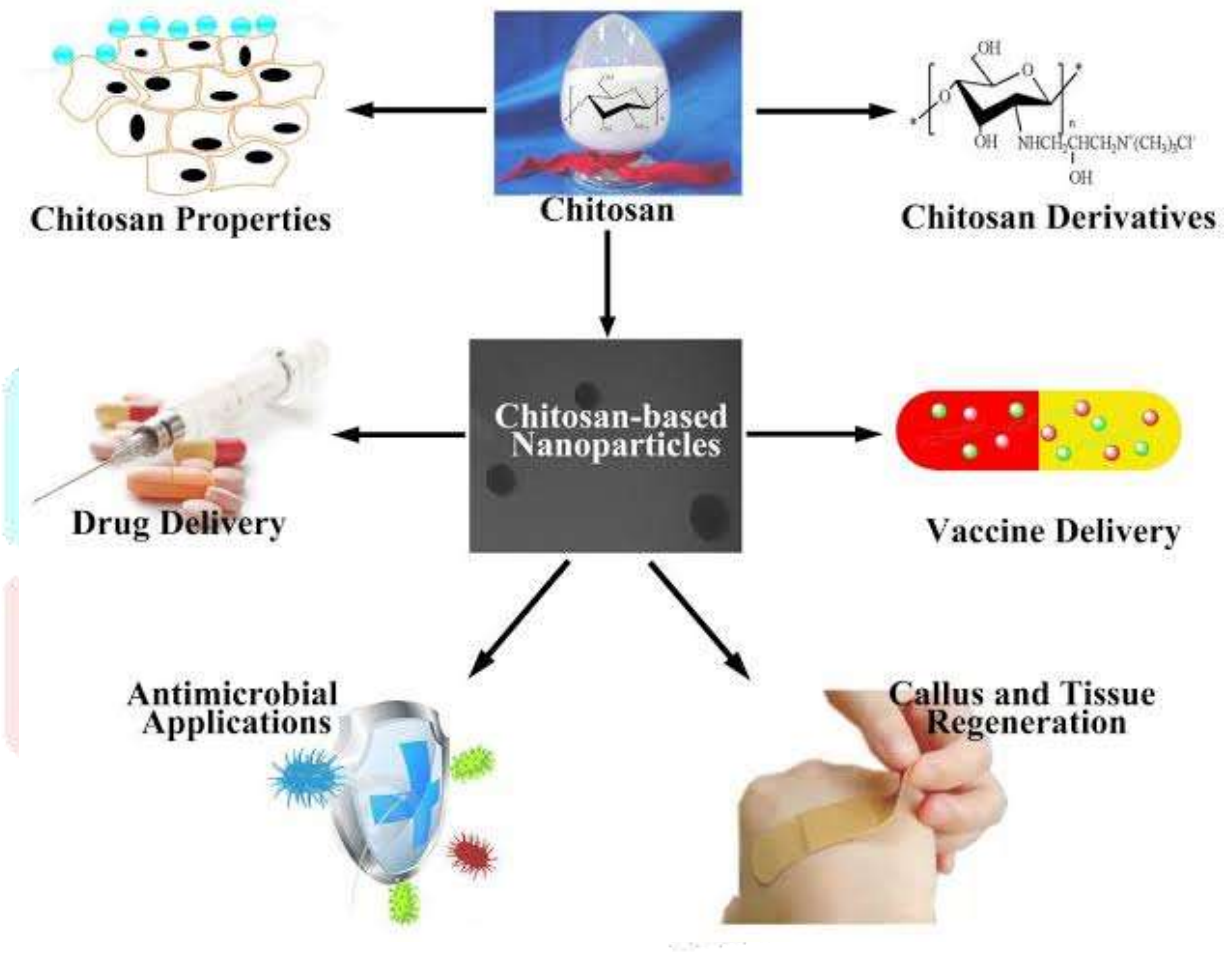

Fig.3 .Chitosan-based Nanoparticles.[29]

There are some fabrication methods for chitosan nanoparticles are as follows.

2.1.1.Inorganic gelatin method

The creation of chitosan-Polyethylene oxide (PEO) nanoparticles via the ionotropic gelation process was initially documented by Calvo et al. [10]. Under the right circumstances, chi-tosan's positively charged amine groups can undergo a sol-gel transition and react with negatively charged polyanion to create nanoparticles [11]. Tripolyphosphate (TPP) is a frequently selected poly-anion [12,13]. Calvo et al. prepared TPP in filtered water with the same concentrations as the chitosan solutions (0.05 weight percent, 0.1 weight percent, 0.5 weight percent, and 1 weight percent) and various concentrations of chitosan in acetic acid aqueous solutions. Mixing different amounts of TPP with the chitosan solutions produced the ideal conditions for creating chitosan nanoparticles. Then, nanoparticles of chitosan/PEO and chitosan/PEO-PPO were fabricated by adding TPP aqueous solution to the chitosan solution which containing PEO & PEO-PPO by constant stirring. in contrast to chitosan nanoparticles, suggesting that the

chitosan/PEO and chitosan/PEO-PPO nanoparticles are more stable. 2.1.2. The solvent diffusion method for emulsification Poly D, L-lactide/glycolide (PLGA) nanoparticles were initially created using the emulsification solvent diffusion process [14], which El-Shabouri modified to create chitosan nanoparticles [15]. Methylene chloride was used to dissolve the medication Cy-A and lecithin before they were added to acetone. After five minutes of high-pressure homogenization and magnetic stirring, the combined solution was added to the aqueous chitosan solution. Low-pressure evaporation, filtration, centrifugation, re-suspension in water, and re-centrifugation were all performed on the suspension. attain a particle size of roughly 150 nanometers.

2.1.3. The technique of polyelectrolyte complex (PEC)

By using the poly-electrolyte complex (PEC) technique, chitosan and DNA can also combine to produce nanoparticles. When their hydrophilicity decreases due to charge neutralization, DNA and cationic chitosan can self-assemble to form nanoparticles [8]. Chitosan/DNA complexes were introduced by Erbacher et al. [16] for the delivery of genes. DNA phosphate was combined with various polymer equivalents to create the complexes. After 15 minutes of incubation at room temperature with continuous stirring, the reaction was finished. The variety of particle sizes was displayed by dynamic light scattering (DLS).between 80 and 500 nm for the 0.5–10 DNA/chitosan ratio. Nonetheless, the particle size ranged from 1 to 5 μm when the zeta potential was near zero. According to transmission electron microscopy (TEM), the complexes were donut- and rod-shaped and ranged in size from 50 to 100 nm. The ionotropic gelation process requires the fewest steps of the three chitosan nanoparticle synthesis techniques,and each step is carried out in a moderate and aqueous non-toxic environments. It is thought to be the most straightforward and useful approach. The use of hazardous solvents and high pressure are two disadvantages of the emulsification procedure, but it is also very helpful when the medicine being utilized is hydrophobic. The PEC process yields nano-chitosan particles with the capacity to transfer genes.

Chitosan nanoparticle applications in medication delivery :

The use of chitosan nanoparticles in cancer treatments has been extensively researched. Through active targeting, passive targeting (also referred to as the increased permeability and retention (EPR) effect [17]), and physical targeting through stimuli-sensitive targeting, chitosan nanoparticles can target tumors on particular organs.

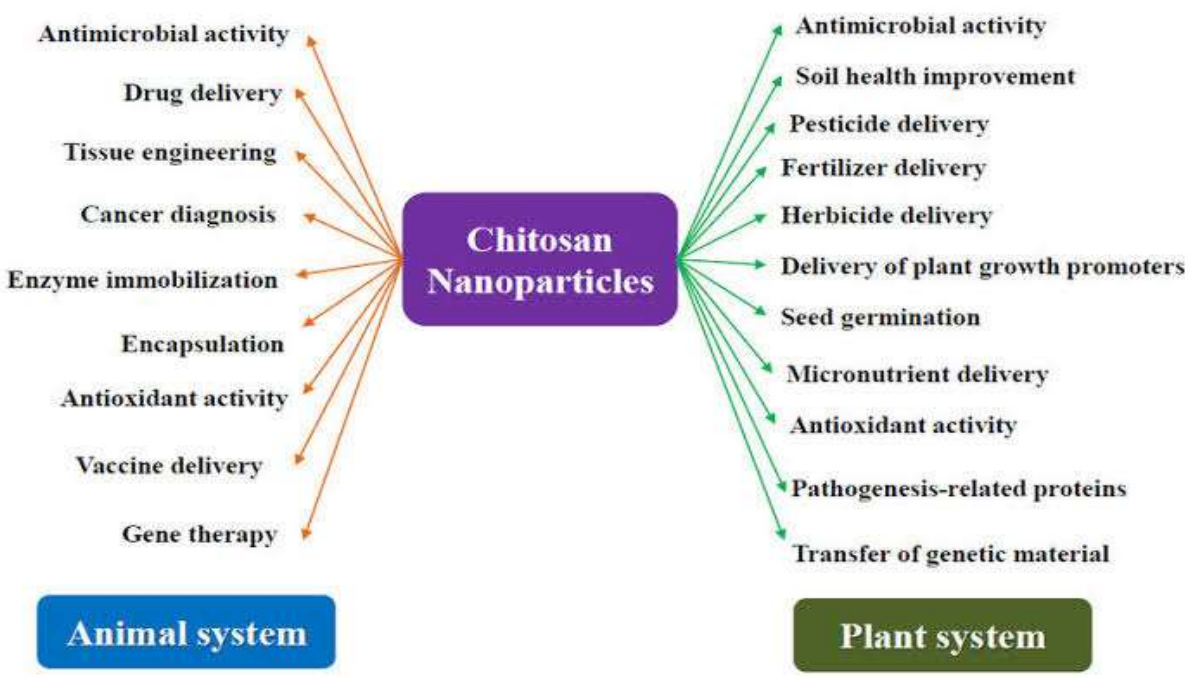

Fig.4 . Chitosan nanoparticles applications in medication delivery[30]

2.2.1. Using chitosan nanoparticles to target tumors passively and actively

Jain and Jain [18] used ionotropic gelation to create hyaluronic acid (HA) linked chitosan nanoparticles. 5-fluorouracil (5FU) was selected as the medication to treat colon cancer. Because there are more HA receptors around tumor tissues, HA was added to the DDS chitosan nanoparticles. As a result, colon cancers can be targeted by nanoparticles through both the EPR effect and HA binding to HA receptors. Following the conjugation of HA with free amino groups on chitosan (Scheme 1), the diameter of the chitosan nanoparticles loaded with 5FU produced in this study rose to around 150 nm. Due to the twofold barrier produced by an extra HA layer on the nanoparticles, HA coupled nanoparticles demonstrated decreased drug release in 24 hours when compared to uncoupled chitosan nanoparticles. The HA-conjugated chitosan nanoparticles appear to be potential vehicles for targeted drug delivery to colon tumors, as evidenced by the increased cell uptake rate by cancer cells during 4 hours of incubation at 37°c . Chitosan nanoparticles for stimuli-sensitive tumor targeting In cancer treatments.

2.2.2 Stimuli-sensitive targeting of tumors using chitosan nanoparticles

stimuli-sensitive chitosan nanoparticles are also frequently employed. Since inflammatory or malignant tissues will show signs of acidosis or hyperthermia, pH and temperature are frequently selected as physiological indicators. A pH-mediated chitosan-based microgel drug delivery system for cancer treatments was designed and described by Zhang et al. [19]. N-[(2-hydroxy-3-trimethylammonium)propyl]chitosan chloride (HTCC) was produced by reacting chitosan powder with glycidyltrimethylammonium chloride after it had been initially dissolved in water at 85°C. HTCC nanoparticles were created by employing the ionotropic gelation technique. approach using TPP. Chitosan nanoparticles' width grew from less than 200 nm to about 400 nm (a 2.2-fold increase) and their relative volume increased by 11 times when the pH dropped from 7.4 to 5.0. It is suggested that the microgels will exhibit significant swelling following internalization into the cell, which will allow them to remain in the sick area and release the medication. The loading efficiency, release kinetics, and cell viability/mortality were assessed following loading with methotrexate disodium (MTX). In contrast to around 30% of the drug, microgels had a quicker drug release rate at pH ¼ 5.0 (93% after day 1). Trapped in microgel at pH ¼ 7.4 after 5 days. When compared to the pure drug group and non-conjugated MTX-chitosan nanoparticles, MTX-loaded HTCC demonstrated the highest mortality on HeLa cells in cell viability tests.: Nanoparticles of silica Drug delivery has made extensive use of silica xerogels as inorganic materials. It is easily functionalized, extremely porous, and biocompatible. Mesoporous silica nanoparticles (MSNs) were initially reported to be fabricated in 1992 by Kresge et al. [20]. When compared to silica xero-gels, MSNs provide numerous benefits for usage as drug delivery systems. i) materials that are made to be nano-sized have a larger surface area (often greater than 1000 m2/g) and pore volume, which makes them better for drug adsorption and loading into the pores [21]; ii) altering the size of the nanoparticles can change the drug loading and release kinetics [22]; iii) surface modification of MSNs is simple and improves the targeting resulting in a decrease in systemic toxicity and an improvement in drug delivery efficacy [23,24]; iv) MSNs can be utilized as bioimaging and drug delivery systems in conjunction with magnetic materials or luminous chemicals.

3. Silica nanoparticles

Drug delivery has been made extensive use of silica xerogels as inorganic materials .It is easily functionalized ,extremely porous,and biocompatible .Mesoporous silica nanoparticles (MSNs) were initially reported to be fabricated in1992 by Kresge et al.[20].When compared to silica xero-gels,MSNs provide numerous benefits for usage as drug delivery systems-i)Materials that are made to be nano-sized have a large surface area (often greater than 1000 m/g) and pore volume,which makes them superior for drug adsorption and loading into the pores [21]; ii) altering the size of the nanoparticles can modify the drug loading and release kinetics [22] iii It is simple to modify the surface of MSNs, which improves the

nanoparticles' targeting capability and raises the effectiveness of drug delivery while lowering systemic toxicity.[23,24] iv)) MSNs can be used as drug delivery systems and bioimaging when combined with magnetic materials or luminescent compounds. Surface modification of MSNs is simple and improves the targeting ability of nanoparticles, increasing drug delivery efficacy and decreasing systematic toxicity [25,26]

Table 1:

List of FDA-approved nonomedicines for cancer treatment. [32,33,34,35]

Tradename	Material	Drug	Company	Indication	Year(s)approved
Doxil®	Liposome-PEG	Doxorubicin	Janseen	Metastatic breast cancer, metastatic ovarian cancer	1995
Eligard®	PLGA	Leuprolide acetate	Tolmar	Prostate cancer	2002
Abraxane®	Albumin	Paclitaxel	Celgene	Metastatic breast cancer,Pancreatic cancer	2005
Genexol PM®	MPEG-PLA	Paclitaxel	Samyang Corporation	Metastatic breast cancer	2007
Onivyde®	Liposome	Irinotecan	Merrimack	Pancreatic cancer	2015

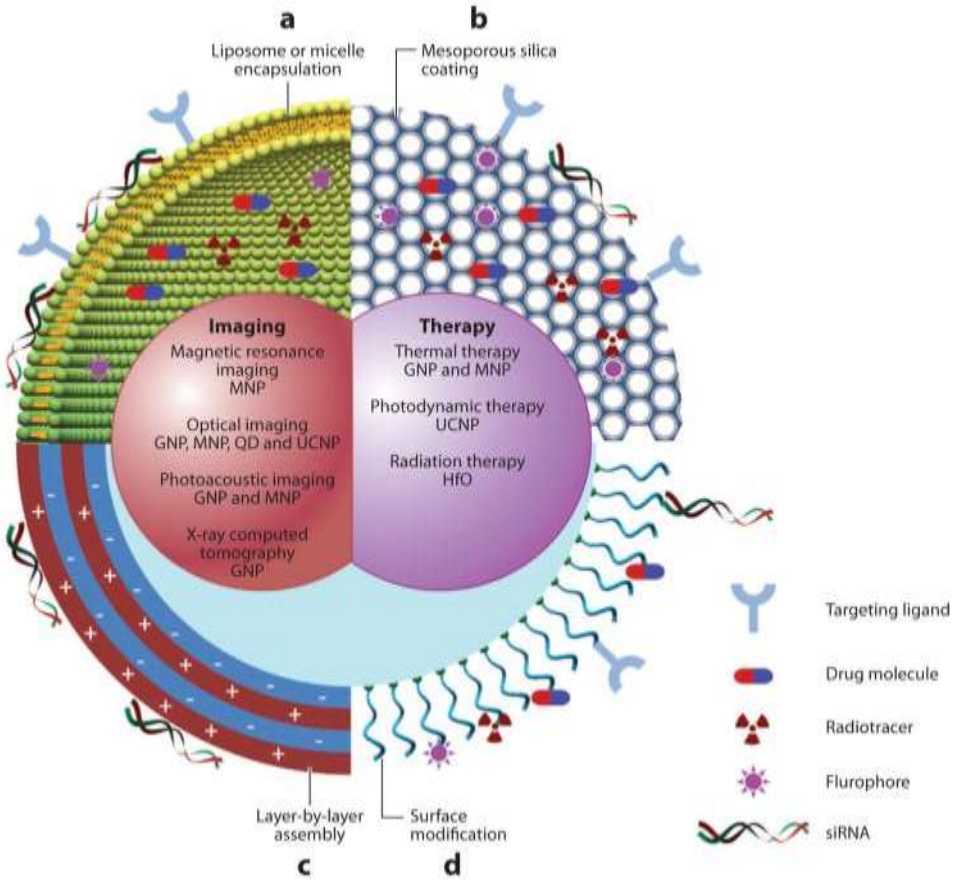

Fig. 5. Schematic diagram of multifunctional nanoparticles. [31]

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