Section A-Research paper

NANOPARTICLES – A REVIEW ON THEIR PROPERTIES AND APPLICATIONS IN TARGETED DRUG DELIVERY

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Abstract:

Nanotechnology is a field of science that deals with the nanosized materials ranging from 1 to 100nm. These nanomaterials are used in various fields such as environment, electronics, cosmetic, medicine, etc. Nowadays, the nanoparticles are widely used in the field of medicine for the purpose of drug delivery as a biological agent, chemotherapeutic agent, imaging system, immunotherapeutic agent, disease therapy, etc. They are also used in drug delivery due to its small size, larger surface area and ability to cross blood brain barriers. Nanoparticle based delivery systems are engineered based on the requirements of the disease and targeted to diseased site by active or passive targeting methods. The aim of the current paper is to discuss the application of nanoparticles in targeted drug. In this current review, various types of nanoparticles and their applications in the field of medicine are discussed.

Keywords: Nanomaterials, targeted drug delivery, drug delivery system.

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1. Introduction:

In recent years nanotechnology plays a major role in the growth of research and applications mainly in the field of medicine for the treatments and diagnosis of numerous diseases. Nanoparticles that are used in the field of medicine should have the larger surface to mass ratio when compared to other particles and should have the ability to absorb and carry other compounds such as drugs, Probes and Proteins. Usually, nanoparticles have the dimensions below 0.1nm or 100nm, but Nano scale devices that are used for carrying the drug should be customized based on dose of the therapeutic agents [1-3]. Nano scale devices are constructed in two ways namely top- down approach and bottom – up approach. In case of top- down approach nanoparticles are synthesized mechanically by breaking bulk materials into several parts whereas, in bottom – up approach synthesis of nanoparticles using chemical reaction among the atoms or ions[4] [5]. Figure – 1 shows the top – down and bottom -up approach for synthesis of nanoparticles [6].

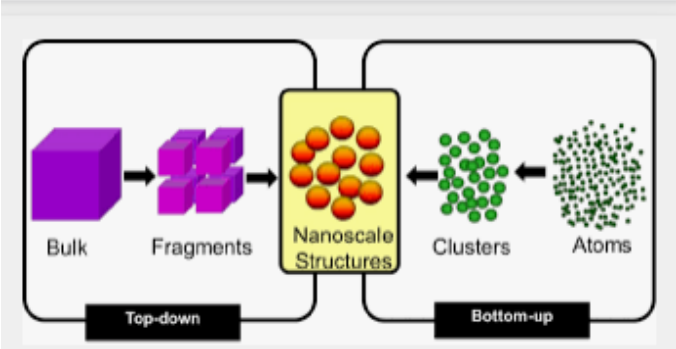

Figure 1 – Top – down and Bottom – up synthesis. Source: Rawat RS (2015)

In case of targeted drug delivery, the nanoparticles are manufactured by bottom-up method and interact with each other using external stimuli (pH, light, temperature, magnetic field and electric field) and self-assemble into complex structure [7]. The drug to be delivered is either encapsulated with nanoparticles or attached to the surface. The drug loaded nanoparticles are transported to the diseased site. There are three methods using which the drug loaded nanoparticles are transported. They are (i) Passive targeting (ii) Active targeting and (iii) Physical targeting. In passive targeting, nanoparticles are coated with PEG, and this coating enhanced the circulation time of the drug loaded nanoparticles to reach the estimated site of delivery [8]. Active targeting is a method in which the nanoparticles are developed more specific to target site. The nanoparticles are combined with the cell specific ligands such as antibodies, proteins and peptides to reach the site of delivery [9]. In case of physical targeting an external source such as photo thermal or magnetic hyperthermia therapy is used to control the release process [10].

Targeted drug delivery can be achieved using several drug delivery vehicles, which needs to be designed in such a way that it's not identified by the defence mechanism of the host, biodegradable, biocompatible, non-toxic, non-immunogenic [11]. Peptides, Liposomes,

Micelles and dendrimers are the few drug carriers which are used for the delivery of the drugs.

The aim of the paper is to review usage of nanoparticles in the field of medicine for the process of targeted drug delivery. In this current review paper we have discussed the application of nanoparticles in targeted drug delivery through various literatures. Initially the concept about nanomaterial, its types and necessity in targeted drug delivery were discussed. Later, the applications of these nanoparticles in targeted drug delivery were also mentioned.

2. Nanomaterials:

The term Nanotechnology was proposed by a nobel laureate named Richard P. Feynman in a lecture entitled "There is a plenty of room at the bottom" from there onwards numerous developments in the field of nanotechnology started. Nanotechnology produces materials at nanoscale. These nanomaterials are measured in terms of nanometre (nm) and represented as 10 -9 nm, their size ranged from 1 to 1000nm in length with one dimension and 1 to 100nm in diameter. According to EU Commission, the term nanomaterials means manufactured or natural materials with unbound aggregated or agglomerated particles with external dimension 1 to 100nm [12]. Nowadays, these nanoparticles and the nano structured materials play major role in the advancement of research due to their physicochemical properties such as electrical conductivity, melting point, thermal conductivity, etc.

2.1. Classification of Nanomaterials:

It is very tricky to classify the nanomaterials as they are prerequisite to express the category specific characters and there are many criteria to classify the nanomaterials. Hence, there is a freedom for the researchers to classify the nanomaterials according to their research. Nanomaterials are broadly classified based on their origin, dimension, chemical composition, and morphology [13].

2.1. a. Classification based on origin:

The nanomaterials are grouped into three categories based on their origin there (i) Naturally produced materials (ii) Incidental nanomaterials (iii) Engineered nanomaterials.

Nanomaterials are naturally present on the microorganisms (bacteria, algae and virus), plants, insects, animals, birds and humans. Nowadays, there are many types of equipment to study the structure of the naturally formed nanomaterials so that they can be used in the biomedical applications. For example, animals and small insects use nanomaterials for the protection against predators and development of light wings made of nanowax coating. Incidental nanoparticles are produced by the volcanic eruption, forest fires, and hair shedding of plants and animals. The volcanic eruption produces a large amount of aerosol into the environment and its size ranges from micrometer to manometer [14]. The activities such as welding, ore refining, smelting and simple combustion at the time of cooking lead to the production of engineered nanoparticle formation [15]. Moreover, the cosmetic (sunscreen) also contains carbon, TiO2 nanomaterials [16] which causes adverse effect on human and environment [13].

2.1. b. Classification based on dimension:

Nanomaterials are classified into four categories based on the dimension. They are Zero Dimensional, one-dimensional, two dimensional, three dimensional [13].

The types and applications of these nanomaterials are given in Table – 1. From that it's clear that three dimensional nanomaterials are used in targeted drug delivery.

Table 1 – Types and Applications of Nanomaterials

Dimensions	Types	Applications
Zero Dimensional	Quantum dots	Electronics
One-dimensional	Nanorods, Nanobelts, etc.	Electronics, Catalysis, etc.
Two dimensional	Nanosheet, Nanofilm & Nanocoatings	Nanostructured devices (Sensors, reactors)
Three dimensional	Fullerenes and dendrimers	Pharmaceutical agent, Nanoreactors, etc.

2.1. c. Classification based on morphology:

Based on Morphology the nanomaterials are classified into various types. Morphology includes shape and size. Shapes of the nanomaterial includes: Sphere, cubic, hexagonal, triangular, oval-shaped, rod, prism like, helical, tube like, etc [17]. Apart from this, there are various intrinsic crystals they are body or face centered cubic, icosahedron, decahedron, simple cubic etc [18].

2.1. d. Classification based on chemical Composition:

Based on the nanomaterials chemical composition there are classified into several types, wherein they are metallic nanomaterials, semiconductor nanomaterials, carbon based nanomaterials, ceramic based nanomaterials, lipid based nanomaterials, polymeric nanomaterials. From various literatures it's clear that, the categories of nanomaterials under the classification based on chemical composition have the vast application in the field of medicine mainly for targeted drug delivery.

3. Targeted drug delivery:

Drug delivery is a method that is helpful in transporting drugs to the body for the specific disease. According to Paul Ehrlich, nanomedicine is an advance version and the concept is known as magic bullet concept. In recent years the drug delivery method is developed in such a way that the drug is delivered in particular time, dose and location with maximum efficacy and safety. Based on the appropriate drug demand, the delivery of the therapeutic components to the specific site is made possible through targeted, sustained and mediated delivery [19]. Targeted drug delivery is considered as the effective system to

deliver drugs, since they deliver drugs at the particular site rather than the whole body. It also involves nanoparticles for their delivery.

In case of drug delivery, there are five generations. Among these five generations, targeted drug delivery comes under the fourth generation [20]. Figure: 2 shows the generations of drug delivery system [21]. The main aim of drug delivery is to target the drug to the site of action, minimize the adverse effect of the drug to healthy tissue, and control the less/over dose of the drug [22].

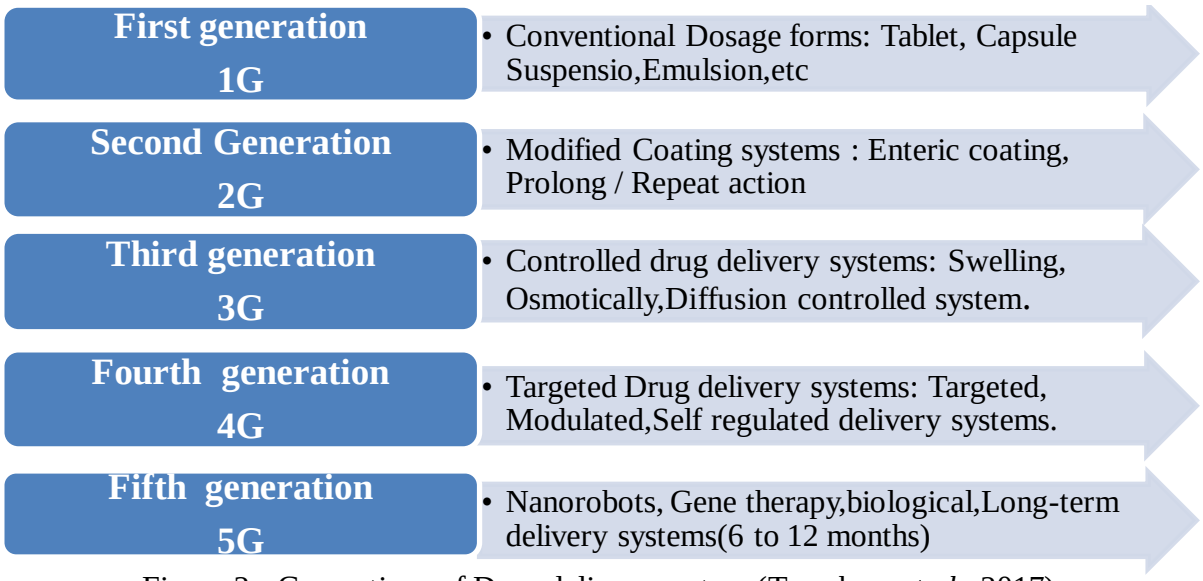

Figure 2 - Generations of Drug delivery system (Tewabae, *et.al.*, 2017)

4. Nanoparticles as drug carriers in Targeted drug delivery:

The magic bullet concept which was postulated by Paul Ehrlich is the main reason for the targeted drug delivery using the nanoparticle. According to him, pathogens can be selectively targeted without harming host organisms using the "magic bullets". In his work, he screened the toxic drugs and modified them to less toxic and more specific to the organisms so that the parasite within the organisms will be eradicated without hurting the human body. Later, this gun hit method of site specific drug delivery, attracted many researchers to develop methods of targeted drug delivery. To establish this method, the nanoscale devices were developed to carry the drug; hence this led to the development nanomedicine [23-24].

Use of nanoparticles was found to be increasing day to day. In order to prove this fact, we would like to highlight the PubMed search of "nanoparticles in targeted drug delivery". Up to date survey denotes that nearly thousands of articles are published every year regarding usage of nanoparticles in targeted drug delivery for various diseases [25]. Data collected from the PubMed site was represented in a graph (Figure-3). Hence, it is clear that the nanoparticles are being engineered and manufactured based on the requirement for the targeted drug delivery.

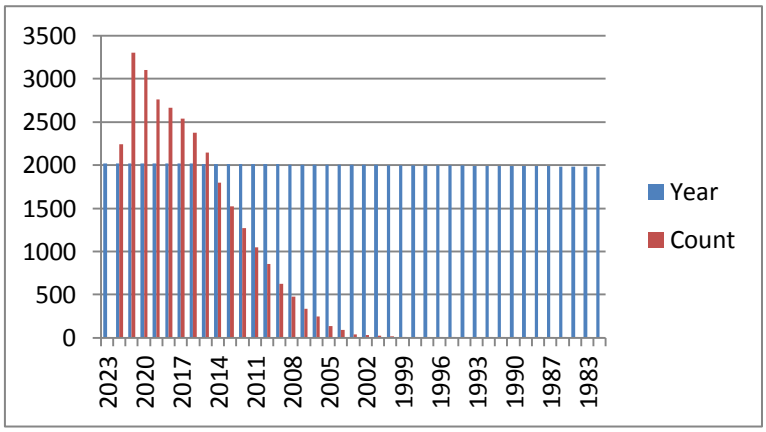

Figure -3.Graph showing the number of research carried up to date.

4.1. Characteristic on Nanoparticles in targeted drug delivery:

The characteristics of nanoparticles such as size, surface properties, shape, and drug loading & releasing capacity were used in targeted drug delivery.

4.1.1. Necessity of Nanoparticles size in targeted drug delivery:

Nanoparticles have a wide range of applications in the field of drug delivery, owing to its maximum efficacy in delivering the drug to the required site. Traditional method of taking medicine either through injections or oral intake is not effective nowadays, since the drug is not prepared with actual formulation requirement and they are also degraded [26]. In order to reduce the degradation of drug, nanoparticles are used in drug delivery. Desirable size and large surface area of nanoparticles make them soluble and enhance its bioavailability to cross the blood vessels and reach the target site without disturbing the activity of the normal cells. The scaffold structures of the nanoparticles are responsible for the attachment of the drug with the help of a ligand to bind to the bio- marker [27].

The nanoparticles used for targeted drug delivery are customized based on the purpose of its usage and also designed for its increased bioavailability and controlled release as per the medications. Size of the nanoparticles decides its fate. Nanoparticles less than 10nm will be vanished by the kidney and the nanoparticles more than 100nm are cleared from the circulatory system by the cells of mononuclear phagocyte system [28-29]. If the nanoparticles are 7nm with hydrodynamic diameter it will fall into the execratory region such as renal filtration and urinary excretion [30-31]. The nanoparticles larger than 200nm are activated by lymphatic system and easily cleared from the circulation [32]. In order to pass through the openings of the tight junctions and reach the target site the nanoparticles are treated with hyper somatic mannitol solution [33].

Thus, from various literature discussions, it is clear that the nanoparticles size decides its fate in drug delivery. Hence, the size of the nanoparticle should be approximately 100nm so that it can pass through the blood – brain barrier and deliver sufficient amount of drug to the site due to its high surface area to volume ratio and this avoid the clearance by the lymphatic system.

4.1.2. Surface properties of Nanoparticles in drug delivery:

Apart from size, surface also plays a major role in the targeted drug delivery. In order to create an ideal system for drug delivery its surface properties are considered. The properties such as stability, surface curvature, reactivity, incorporation of appropriate ligands, pharmacological effect of the drugs are needed for creating nanoparticle based drug delivery system [34]. Even though nanoparticles are created based on the requirements, it is identified by the lymphatic system as foreign matter and cleared by body‘s natural immune response. As the nanoparticles are hydrophobic in nature, with higher binding of blood components they are easily cleared [35]. Hence, by changing its surface nature as hydrophilic, its circulation time in blood can be increased.

Surfactants or copolymers are the materials used for coating the nanoparticles. Various copolymers such as Polyethylene glycol, polyethylene oxide, polyoxamer, polyoxamine and polysorbate 80 are considered as the valuable materials. Among these polyethylene glycol has hydrophilic property and prevents the nanoparticles from clearing (opsonisation) so the given dose can reach the target site. One more difficulty found in drug delivery is the aggregation of nanoparticles due to its small size and large surface area. This can be rectified by coating the nanoparticles with the capping agents (dendrimers, small ligand, surfactants, polysaccharides and cyclodextrins) and by altering its surface charge (zeta potential) [36].

Internalization of particles into cancer cells is not possible even after increasing its circulation time or overcoming aggregation of nanoparticles and then this problem was solved by active targeting (addition of tumor- specific ligand) to the surface of nanoparticles [37]. Therefore, all the surface properties and problems regarding targeted drug delivery to specific site can be reduced as per the ideas mentioned above from other literatures.

4.1.3. Shape of the nanoparticles in drug delivery:

Usually nanoparticles occurs in spherical, cubic, rod, tube, helical, triangular, fibres, plate, hexagonal, oval and prism shapes [17]. Among these nanoparticles sphere, cube, rod and plate shaped nanoparticles plays a major role in the targeted drug delivery. Sphere shaped nanoparticles are widely used for internalization of the drugs due to their (i) increased circulation time in the body (ii) endocytosis of sphere shaped nanoparticles are faster [38] (iii) less toxic (homogenous or heterogenous) [39].

HeLa cells absorb more gold spheres when compared to the gold rods [40]. Internalization of the drug to the site is possible if the axis particles are placed perpendicular to the cell membranes. There are several reports that show the advantages of rod shaped nanoparticles over sphere shaped nanoparticles [41]. The uptake of gold nanorods is higher than the gold sphere [42]. Similar works were performed in the rod shaped SWCNT blocks the K + ion channel more efficiently than the spherical carbon fullerenes [43].

Several studies have shown the shape dependent toxicity in many nanoparticles during drug delivery. In case of fibres, TiO_2 fibres were found to be more toxic when compared to spheres

[44]. This is because long fibres are not cleared from the respiratory tract through phagocytosis. By taking this in consideration the work was performed on TiO_2 fibres in mice and given the report that long fibres with 15nm are highly toxic when compared to the 5nm fibres and it showed the inflammatory response in the alveolar macrophage of mice. The soluble fibre will be removed by the lung fluids after several months while insoluble fibre remain in the lung as such, so this may not be safe [45]. Further, works were also studied using both long MWCNTs and short MNCNTs, in this case long MWCNTS shows inflammation on the abdominal walls after intra-abdominal instillation while short MWCNTs doesn't show any inflammatory responds [46].

From these literatures it's clear that shape of the nanoparticles plays major in targeted drug delivery with certain impacts, so that it is necessary to develop a safer nanoparticle based drug delivery system.

4.1.4. Drug loading – releasing capacity:

Nanoparticle delivery systems that are designed based on the requirement should have high drug loading capacity. The entrapment efficiency of the drugs depends on the polymer composition, interaction between drug and the polymer, molecular weight, presence of the functional group. The drug loading can be done using two methods they are:

i) Incorporation method – The nanoparticles are incorporated at the time of production. Nanospheres are loaded with drugs, the drug will be uniformly distributed and the release occurs through diffusion of the matrix in sink conditions [47]. The mechanism of drug release will be controlled by diffusion process, when diffusion of drug is faster than the matrix erosion. Drugs absorbed on the larger surface of the nanoparticle cause initial release or burst of the drug. This is the evidence for the incorporation of the drug through incorporation method because drug loaded by incorporation method causes small burst effect and has better sustainable characters [48].

ii) Absorption / Adsorption Method - The concentrated drug solution is incubated with the carrier after formation of nanoparticle to absorb the drug [49]. PEG moiety has no effect or little effect on drug loading [50].

Apart from drug loading, the polymer degradation and drug release are two factors that should be considered for the development of the drug delivery system. The drug release is governed by factors like nanoparticle matrix degradation, drug diffusion through nanoparticle matrix, solubility of the drug, combination of the diffusion process, desorption of the surface bound drug, biodegradation of the matrix materials. If the drug is coated with polymer membrane, then the membrane will act as barrier for drug release, hence solubility and the diffusivity properties of drug act as the determine factor of the drug release.

In order to reduce the burst effect during drug release, the drug can be coated with the auxillary ingredients so that the ionic interaction between the drug and the auxillary ingredients causes the formation of less water soluble complex, due to this the drug release will be very slow with no burst effect [51]. Later this was explained in a research by addition

of PEO-PPO (ethylene oxide-propylene oxide) block copolymer to chitosan (matrix material) reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material due to the competitive interaction of PEO-PPO with chitosan then causes the increase in drug release [52].

5. Applications of nanoparticles in targeted drug delivery:

5.1. Metallic nanoparticles in targeted drug delivery:

Metallic nanoparticles have a major role in the field of medicine as the nanocarriers for various treatments to deliver the drug to the specific site by means of active and passive targeting. Metallic nanoparticles are synthesized either through top down or bottom up approach using physical, chemical and biological methods. The nanoparticles synthesized by physical and chemical methods produce hazardous by products, in order to reduce the toxicity the nanoparticles were synthesized by means of biological or green method and this method was considered as eco-friendly. Metallic nanoparticles such as gold, silver, copper, zinc, titanium, palladium and chromium are used for targeted drug delivery because their surface are functionalized to tag the therapeutic agents and biomolecule by H-bonding, Covalent bonding and electrostatic interactions [53]. Few examples of the usage of metallic nanoparticles for drug delivery were discussed below.

5.1.1. Silver Nanoparticles:

Silver nanoparticles synthesized using honey bees were used as carrier to treat colon carcinoma Caco-2 cells. The AgNPs are used in the concentration of 39µg/mL with 60% inhibition of Caco-2 cell proliferation [54]. The activity of acute myeloid leukemia (AML) cells activity was found to be reduced by the PVP-coated AgNps effectively by stimulating the DNA damage and apoptosis by generating the reactive oxygen species and the release of silver ions [55].

AgNps are prepared by coating them with graphene oxide as doxorubicin nanocarriers (Ag- NGO-DOX) has the potential to release the drug at the target site intracellular acidic pH release of DOX, which was responsible for the drug to reach the nucleus of the cancer cell (HepG2 and HEK293 cell line) [56].

5.1.2. Gold Nanoparticles:

Gold nanoparticles are used in drug delivery for the treatment of cancer, bacterial infections, diabetics and inflammation, etc. The gold nanoparticles have the capacity to release multiple drug molecules, proteins, Vaccines, recombinant proteins into the specified target site.

In vivo targeting of AuNps to breast cancer was developed using herceptin to functionalize the AuNps by molecular recognition of breast cancer cells along with PEG [57]. Two types of glucose responsive high drug loading gold nanoclusters (AuNCs) were used for insulin release. The first type of AuNCs were synthesized based on the CR 9 peptide and couples with 4-carboxy-3- fluorophenylboronic acid (FPBA-COOH) and insulin molecule to

obtain AuNCs complex drug(CR9-AuNC-PBA-Ins), and the second type AuNCs were synthesized based on bouvine serum albumin(BSA), carboxyl enriched BSA-AuNCs are coupled with 4-aminophenylboronicacid (NH2-PBA) molecules and insulin labelled as BSA-AuNC-PBA-Ins a micro needle (MN) patch was loaded to the AuNC nanocomplex drug. The treatments for type 1 diabetics were reported by soluble and glucose-responsive insulin releasing MN patch system. They fused MNs with high drug loading AuNC nanocarriers; the gold nanomaterials enhance the mechanical strength of MNs to penetrate the skin of the mice [58].

5.1.3. Copper Nanoparticles:

Copper nanoparticles were used due to their physical, chemical, electrical and optical properties and low cost of availability compared to gold and silver. The curcumin capped CuNps were used as the inhibitors of human breast cells and angiogenesis using native curcumin [59].

Transferrin (Tf) modified hollow mesoporous CuS nanoparticles (HMCuS Nps) diffuse through the interstitium and tumor retention after peritumoral injection (PT).The iron dependent artesunate (AS) has the cytotoxicity against tumor cells were used as the drug model [60].

5.1.4. Zinc Nanoparticles:

Zinc oxide nanoparticles is one of the most commonly used and produced nanomaterials. They are mainly used for their biocompatibility, economic and low toxicity properties. These nanoparticles are used as the anticancer, antidiabetic and antibacterial agents. Zinc oxide nanoparticles help in triggering excess reactive oxygen species (ROS) and produce zinc ions that induce cell apoptosis.

PEG-modified ZNO Nps kills the breast cancer cells. In this study, PEG-modified ZNO Nps were found to be active against breast cancer line cells. The PEG-modified ZnO kills the cancer cells by generating ROS and triggering p53-dependent apoptosis [61].

The Zno nanoparticle also acts as the antibacterial agent. Ph β-GBP-Zno coated nanoparticles were prepared from haemolymph of *Paratelphusa hydrodromus* by extracting crustacean immune molecule β-1, 3-glucan binding protein (Ph β-GBP). The Phβ-GBP-ZnO was found to be the spherical shape nanoparticle with size 20-50nm. These nanoparticles restrained the growth of *Staphylococcus aureus* and *Proteus vulgaris* among both *Staphylococcus aureus* was found more susceptible to Phβ-GBP-ZnO NPs than *Proteus vulgaris*. The Phβ-GBP-ZnO Nps alters the cell permeability and triggers high level of ROS formation in both the organisms. Hence, it was proved that Phβ-GBP-ZnO NPs could act as the antibacterial agents [62].

5.1.5. Platinum Nanoparticles:

Platinum itself has the anticancer property. The platinum nanoparticles immediately after entering the body through passive diffusion or endocytosis cause cytotoxicity due to the

introduction of strand breaks in the chromosomal DNA. The DNA damage arrests induction of cell cycle, inhibition of replication and apoptosis [63].

The malignant bone cancer therapy was performed by targeting the bone with platinum nanoparticles (PtNPs) coated with phytic acid (PA) through photo thermal therapy [64]. In Vitro assay of PA/PtNPs showed the binding affinity for hydroxyapatite and bone fragments, in addition to intrinsic antitumor activity. Later the in vivo bio distribution analysis shows the accumulation of PA/PtNPs in cancer related bone lesions. Hence, it was clear that the PA/PtNPs effectively inhibit bone cancer and decrease osteolysis.

5.1.6. Ceramic Nanoparticles:

Nowadays ceramic nanoparticles are also used as the drug delivery vehicles due to their small size and physiochemical properties. The size of the nanoparticles is less than 50nm with magnetic, specific optical and electrical properties, which make them suitable for drug delivery. Aluminium oxide and Titanium dioxide are the commonly used nanoparticles for drug delivery.

Aluminium oxide nanoparticles were used in the form of nanotubes containing Thapsigarin. The nanoparticles were fabricated using anodisation process and loaded with Thapsigarin along with autophagy inhibitor (3-methyladenine) to target the autophagy signalling in both normal and cancerous cells. The Thapsigarin-loaded Aluminium oxide nanotubes induced cytotoxic effect and autophagy signalling in cancerous cells, while no effects were noted in the normal cells. This indicates the capability of aluminium oxide nanotube as the drug delivery vehicle for cancer therapy [65].

The anticancer activity of paclitaxel when attached to modified hydroxyapatite (Hap) and TiO_2 nanoparticles in diethyl nitrosamine (DEN) induced heptacarcinoma in animal models. Polyethylene glycol (PEG) was used as the immunogenic polymer and folic acid as the tumour marker to modify the surface of the nanoparticles. The haematological and biochemical results showed the higher anticancer activity of the surface-modified paclitaxel attached to Hap and TiO_2 particles in comparison to pure paclitaxel [66].

5.2. Semi-conductor nanoparticles in targeted drug delivery:

The semiconductor nanoparticles are considered as the semiconducting materials at nanoscale. They have the electrical conductivity higher the conductor and lower than an insulator. The size of the nanoparticles ranges from (1 -20nm), with high surface area and quantum effects.

Quantum dot nanoparticles are considered as the semiconductor particles with optoelectronic and magnetic properties. These quantum dots have high fluorescence and photoluminescence properties. Due to these properties the quantum dots were tested for diagnosis [67] and the trials were carried out for the drug delivery [68]. Later this was found to be beneficial for the radiation, chemotherapy and ionizing radiation imaging for cancer treatment.

The quantum dots are used to target doxorubicin drug to human lung cancer cells. They developed the targeted drug delivery system based on the Ag-In-Zn-S quantum dots. The QD crystals were modified with 11-Mercaptoundeanoic acid (MUA), L-cysteine and lipoic acid and decorated with folic acid for targeting the doxorubicin (DOX) to folate receptors (FARs) on adenocarcinomic human alveolar basal epithelial cells (A549). NIH/3T3 was used as the FAR- negative control. Later the FT-IR confirms the attachment of FA to QD nanocrystals and DOX to the QD-FA nanocarriers. UV-VIS analysis was used for determining the amount of FA and DOX anchorage to the QD nanocrystals. Biological screening of QD-FA-DOX nanoconjugates had higher cytotoxicity when compared to the other forms of synthesized QD samples. The QD-MUA-FA-DOX was considered to be most cytotoxic against A549 cells among others and no effects were noticed in NIH/3T3 cells. Even the in vitro scratch assay reveals the inhibition of A549 cell migration after treatment with QD-MUA-FA-DOX. Hence the QD-MUA-FA-DOX nanoconjugates are considered as the potential drug delivery system for the treatment of adenocarcinomic human alveolar basal epithelial cells [69].

5.3. Carbon based nanoparticles for targeted drug delivery:

The carbon based nanoparticles are used for targeted drug delivery in medicinal field due to their mechanical, electrical, optical, thermal and chemical properties. The carbon has diverse allotropes such as amorphous carbon, graphite and diamonds. The carbon nanotubes, graphene oxide, graphene quantum dots, fullerene are the carbon based nanoparticles [70].

5.3.1 Carbon nanotubes:

Carbon nanotubes are the large molecule, formed by the repeating pattern of sp2 hybridized carbon atom in a hexagonal arrangement, which is wrapped into cylindrical shape with approximate size of 2.5-100nm in diameter. They have the capacity to penetrate the cells and deliver drug directly into the cytoplasm or nucleus. Carbon nanotubes are considered as the best platform for to deliver drugs because, it has variety of biomolecules such as proteins, antibodies or DNA to deliver the loaded dry to the targeted OD specific cells, tissues or organs [71].

The polyvinyl alcohol-functionalized MWNTs when loaded with water soluble anticancer camptothecin were found to be effective for the treatment of breast and skin cancer [72]. The anticancer activity was shown in paclitaxel when loaded into PEGlyated SWNTs or MWNTs using HeLa cells and MCF-7 cancer cell lines [73]. Carbon nanotubes are used for targeting the lymph node can cancer, the researchers used the magnetic nanoparticle containing anticancer cisplatin were entrapped into the folic acid functionalized MWNTs. The drug was moved to the lymph nodes by dragging the drug using an external magnet, later the drug was released in to the tumour site within several days [74-75].

5.3.2 Graphene oxide:

Graphene is a two dimensional material with uniform flat monolayer of carbon atoms packed tightly in a hexagonal or honey comb structure. The grapheme and its derivatives are

used for the biomedical purpose due to its biocompatibility, large surface area and optical properties.

GO-coated Fe3O4 nanocomposites are used for MRI and DOX delivery using the folic acid (FA) targeted system. The FA- Fe3O4@nGO-DOX is the stable material used for targeted drug delivery. The cell viability was conducted and exhibited by cellosaurus cell line/MGC-803 selective uptake to investigate the FA- Fe3O4@nGO-DOX nanoplatforms. As a result, the pH mediated drug release and selective uptake of the nanoparticles through MSC-803using folic acid receptors kill the selective tumour cells [76].

The Graphene oxide (GO/hydroxyapatite (HAP) /chitosan composite (CS) were loaded with cisplatin (CDDP).These structures hinder the osteosarcoma cells development and enhance osteoblast cell growth. The nanocomposite GO/HAP/CS-3/CDDP revealed higher cytotoxicity against cancer cells and high viability on osteoblast like cells; hence it can be used for the replacement of cancer affected bones [77].

5.3.3. Graphene Quantum Dots:

Graphene quantum dots (GQD) - cross linked chitosan were loaded with a model drug (sodium salicylate) and encapsulated in carboxymethyl cellulose(CMC).The nano composites show the stable and controlled drug release pattern in the gastrointestinal track [78].

The embedded grapheme quantum dots/GQDs on carboxymethyl cellulose (CMC) hydrogel film shows high capacity in loading DOX and long release pattern. These films show minor toxicity against blood cancer cells (K562) when it was asserted with DOX-loaded CMC/GQD nanocomposites and exploit as proper anticancer material. The healing and inflammation of wound was treated with GQD. The GQD with fluorescent emission capability along with Chitosan aerogel coating by sodium salicylate are used as the drug for curing wounds [79].

5.3.4. Fullerene:

Fullerene is considered as the pioneer class of carbon based nanoparticles for targeted drug delivery. It has a unique structure consisting of sp2 carbons present in a highly symmetrical cage with different sizes (C60, C76, etc). C60 is the most commonly used fullerene. It has different characteristics of dual behaviour; the reactive oxygen species (ROS) gave this nanoparticle the ability to act in two ways at specific situations. The C60 has the ability to produce oxygen species on exposure to visible light and make it suitable for photodynamic therapy (PDT). The other case is it down regulates ROS, when used as neuroprotective agents. This case is still in further investigation [80].

The complex of fullerene and hexamethonium was developed and compared with hexamethonium deliver system. The results obtained shows 40-times boosted potency in the complex drug delivery system [81]. The fullerenes also have the ability to inhibit HIV-1 protease activity. The Asp-25 and Asp-125 standing out on the surface cavity, keeps the active site semi-open hydrophobic ellipsoid by catalysing the protease function. Hence, the

antiviral activity was caused by the entrance of fullerene into the pocket by attaching to the active site through Vander Waals interactions [82].

5.4. Protein -based nanoparticles in targeted drug delivery:

Protein based nanoparticles are different from other nanoparticles in case of drug delivery due to their biodegradability, biocompatibility and low immunogenicity. During the time of drug delivery, the drugs are combined to the nanoparticles in three ways there i) conjugated to endogenous protein carriers ii) conjugated to modified proteins, iii) combined platforms relying on the protein motifs to deliver the drug to specific site. The types of protein based nanoparticles include albumins, ferritin, collagen, silk proteins, and virus like protein.

5.4.1. Albumin:

Albumin is the most abundant protein present in the blood vessels. It has the property of long term circulation in blood, biodegradable and soluble in nature. The bovine serum albumin (BSA), oval albumin (OA) and human serum albumin (HSA) are the types of albumin.

Abraxane is one of the FDA approved and clinically tested drugs for metastatic breast cancer. These drugs can inhibit the growth of the tumour cells by supressing the mitosis of the breast cancer cells. By using the human protein albumin also avoid the hypersensitivity cause by the previous drug solvents used (Cremophor EL) [83].

The pharmacokinetics and the biodistribution of bufalin–loaded bovine serum albumin nanoparticles showed the prolonged half -life of the bufaline, which is a cancer drug for more than 6hr so that its clearance can be reduced and made it easy for the ingestion of the liver [84].

5.4.2. Ferritin:

Ferritin is a blood protein that contains iron in it and helps to maintain iron level in the person's body. The two types of ferritin are heavy and light, which complement each other. This Ferritin has the ability to bind with the transferrin receptors which allow them to be internalized by the tumour tissues. Due to this property ferritin can be used to deliver drugs [85].

Ferritin can be biologically modified by genetic recombination techniques [86]. The ferritin based lung inhalation delivery systems were used to penetrate lung mucus and target the lung tumour disease. In their work, the human ferritin was functionalized with PEGs. The FTn/FTn-PEG2k particles are the two subunits of both PEGylated (for mucus penetration) and unPEGylated (targeting tumour transferrin receptors. On intratracheal administration of the drug was found to be 78% distributed on the lung tracheal surfaces and it retained in the upper airways for 10minutes. Later these particles were conjugated with doxorubicin molecule, which led to 60% of survival after 60days in a mouse infected with cancer as a model was compared with the free doxorubicin which showed 18 days of survival [87].

5.4.3 Collagen:

Collagen is a type of fibrin that is present in the body (bones, tendons, muscles and skin) which contains almost 30% of the all types of protein. The properties such as notable strechability, tensile strength, absorption in-vivo capacity, weak antigenicity, and biomimetic nature make them suitable for tissue engineering and drug delivery. It acts as the carriers for various agents such as protein, genes, drugs and growth factors.

The collagen based nanoparticles has the ability to reduce the systemic toxicity of the drug and enhance the uptake of nanoparticles by the cells [88].

The collagen nanoparticle is helpful for the tumour infiltration and the anticancer drug delivery. In this study the developed the collagen based tumour spheroids and optimized them using 95-D, U87 and HCT116 cells. Using this model, the antitumor and the drug efficiencies of the drug-conjugated nanoparticles were studied by cytotoxicity and its uptake studies. As a result of this, the conjugated nanoparticles reach the tumour cells by perforating into the gel matrix. Later this model was found be easier to figure out the therapeutic results and dynamic of the drug transport agents by in-vivo method and helps to discover drug fastly for cancer therapy [89].

5.4.4. Silk Protein:

Silk proteins are naturally derived from silk worm cocoon and spider silk proteins. The two types of natural silk are silk fibroin and sericin. The biodegradability, biocompatibility and low immunogenicity are the useful properties that make the silk fibroins suitable for drug delivery. Moreover, the silk protein nanoparticle shows high affinity toward drugs and promotes controlled release, and prepared facilely which make the protein a strong candidate as the drug carriers for cancer therapy.

The works were carried out in silk fibroin to develop the targeted drug delivery system using gemcitabine so that it induces tumour model in mice. In this study, SP5-52 peptides were conjugated with silk fibroin nanoparticles (SFNPs) were used for the systemic administration of gemcitabine to lung tumour. The SP5-52 peptide has the ability to direct the anti-cancer drug carriers to non-small cell lung cancer cells (NSCLCs) [90].

5.4.5. Virus like particles (VLPs):

Viruses like particles are viral proteins that mimic the virus so that lacks the viral genetic materials. They are also known as the self–assembling nanoparticles these particles are produced in variety of systems such as plants, animals, bacteria and insects. This can be used as the carriers for the delivery of nanomaterials such as proteins, nucleic acids, drugs, vaccines and other chemical compounds. VLPs are used as the drug delivery vehicle due to their versatile nature of modifying their own physical properties to suit it to the specific application (genetic manipulation of the sequence coding coat proteins). VLPs are developed from enveloped viruses (Avian sarcoma leucosis virus (ASLVs), HIV-1 viruses, etc.) and non-enveloped viruses (Blue tongue virus) are used for targeted drug delivery of proteins [91- 92].

Cargo proteins are inserted into the VLPs with a protease-cleavable linker to transport and release into the target site. In the year 2019, the cleavable linker were used to optimize the cargo and MLV gag protein to enhance the cargo release and tested the NES/NLV localization and cargo packaging efficiency. They also developed the base editor engineered VLPs (BE-eVLPs), it could deliver base editors fused to Cas9 (184kDa) into the cell nuclei to modify genes in cultured primary cells or CNS cell in animals [92].

The engineered HBc-VLPs targeting the HER2 expresses on the surface of cancer cells and carry siRNA to knock down the polo-like kinase 1(PLK1) gene in the cultured cancer cells and induces the death of the tumour cells.

5.5. Lipid based drug delivery system:

Lipid based nanoparticles are also the carriers for drug delivery. The higher biocompatibility and versatility characteristics of the lipid nanoparticles are the main reason for its usage as the drug delivery system. Moreover, the lipid based nanoparticles can be customized based on the requirements of the disease conditions such as efficacy, product stability and cost, toxicity and route of administration. The liposomes, Solid liquid nanoparticles (SLN) and nanostructured lipid carriers (NLC) are the frequently used lipid based nanoparticles in drug delivery. All these lipid based nanoparticles have the ability to increase the time of drug action, control the drug release and transport hydrophobic and hydrophilic molecules [93].

5.5.1. Liposomes:

Liposomes are widely used as the drug delivery systems for its biocompatibility, biodegradability, ability to carry more drug and self-assembling nature. The conventional liposomes, Sterically-stabilized liposomes, ligand targeted liposomes and theranostic liposomes are the four types of liposomes essential lemon for drug delivery.

The conventional liposomal formulation reduced the toxicity of the compounds in vivo by modifying the pharmacokinetics and biodistribution to enhance the drug delivery to diseased tissue to free the drug [94-95]. The steric stabilization of liposomes suggested that the half-life period of the drug can be increased by coating them with polymer [96]. Ligand targeted drug delivery are helpful to deliver the drug to specific site (cell type or organs) [97].

5.5.2. Solid Lipid nanoparticles:

Solid lipid nanoparticles are generally spherical in shape with the diameter of 50 to 1000nm. The solid liquid nanoparticles are made up of lipids, emulsifiers, mixture of lipid and emulsifiers, active pharmaceutical agent and adequate solvent system. These nanoparticles enter the body through intravenous application due to their effortless dispersion in solution.

The pharmacokinetics was studied on rats and in that study he compared the concentration of doxorubicin in solid lipid nanoparticle with the conventional commercial

drug and concluded that the higher concentration of drug was found in the lugs, spleen and brain of the rats [98].

The efficiency of two-tail cationic lipid and one-tail cationic lipid particles were experimented for gene mediated transfer, the greater transfection efficiency and tolerability was found to be higher in the one tail cationic lipid. [99].

The niclosamide loaded solid lipid nanoparticles, improved the cell uptake and anti-cancer efficacy against the triple negative breast cancer cells [100].

5.5.3 Nanostructured lipid carriers (NLCs):

The Nanostructured lipid carriers are formed by the combination of the solid and liquid lipids. This system has higher drug loading capacity with the nanoparticle size ranging from 10-1000nm. The main advantages of these nano structured lipid carriers are hydrophilic and hydrophobic nature of the drug, site specific targeting, and control release. The nanostructure lipid carriers are used for the prostate cancer therapy when combined with the lipoic acid and ellagic acid [101].

The dissolution rate of the bicalutamide (anticancer agent) which was poorly soluble in water (5mg/l) resulting in low oral bioavailability was improved by Kumbhar and Pokharkar. Hence, the drug release of bicalutamide –loaded NLCs was higher that is 62.08% in 24h in comparison to a drug suspension. Initially it was only 21.99% of drug [102].

Nanostructure lipid carriers act as the delivery vehicle capable of protecting the premature drug degradation during the transport across GIT due to first pass metabolism. The bile salt in GIT interacts with NLCs to form mixed micelles to selective lymphatic uptake bypassing the liver. The mixed micelles promote luminal solubilisation of lipid digestion products and provide concentration gradient for absorption. The versatile capability of NLCs of bypassing liver helps to improve the therapeutic efficacy of drug undergoing extensive hepatic metabolism and decrease their dosing frequency along with dose related effects [103].

NLCs have the ability to overcome problem of multiple drug resistance associated with long-term administration of chemotherapeutic agents. In order to explain this, the NLCs were prepared by combining doxorubicin (DOX) and Vincristine (VCR) to overcome resistance after chemotherapy and the potential for relapses in lymph cancer. The incorporation of the both drug with NCL shows the prolonged and sustainable release of the drug with antitumor effect during tumour progression for about 16hrs (DOX) and 48hrs (DOX) respectively. Later the drug solutions and DOX-NLC, VCR-NLC, DOX-VCR-NLC were compared in lymph cancer animal model. The results showed the DOX-VCR-NLC exhibited more controlled release with synergistic effects and potent antitumor activity by the inhibition of B-cell lymphoma. Hence, the high loading capacity of NLCs formulation offered multiple solutions by combining the chemotherapeutic agents with the same NCL particle shows a control release of both drugs and enhance anticancer effects in the cell [104].

5.6. Polymer-based nanoparticles in targeted drug delivery:

Polymers play a major role in the advancement drug delivery to deliver the drug at constant dosage for long time, cyclic dosage, and release of both hydrophilic and hydrophobic drugs. Polymer based nanoparticles are made from natural or synthetic polymers smaller than 1µm in diameter. Although the drug delivery has developed nowadays still its entry into body such as brain remains difficult. Hence, the carrier mediated transportation of the nondrug delivery system across the blood-brain barriers provide rational drug to control and distribute the drug, so such delivery can be mediated through polymers [8]. The polymers use for the formulation of nanoparticles includes chitosan, Polyethylene glycol (PEG), Polyglycolic acid (PGA), Polylactic acid (PLA), Poly (D, L-lactide-co-glycolic) acid (PLGA), Polycaprolactone (PCL) [105].

5.6.1. Chitosan:

Chitosan is the derivatives of chitin, which are usually derived from crustacean shells of prawn, crab and cell wall of fungi. It is also considered as the FDA approved polymer for drug delivery. Moreover, chitosan also acts as the penetration enhancer by opening the tight junction of the epithelium for the cellular transport of the drug.

Carbamazepine was used for the treatment of epilepsy, which was an important dug to cross the blood brain barrier. It was found that the carboxymethyl chitosan Nps of carbamazepine enhance the bioavailability and brain targeting through nasal route. The results showed that the brain to plasma exposure ratio was 150% when Carbamazepine was administrated as the chitosan Nps intranasal [106].

Tamoxifen is an anti-cancer drug through oral cancer delivery. The permeation of the tamoxifen across the intestinal epithelium can be increased by formulating the tamoxifen into lecithin-chitosan nanoparticles [107].

5.6.2. Polyethylene glycol (PEG):

PEG is the frequently used polymer in all drug delivery methods due to their properties such as flexibility, water solubility and non-charge.

The hyper vascularity of solid tumours enhances the permeability of the PEG-protein conjugates. Later, the transferrin (Tf)-conjugated shows higher effect on human erthroleukemia (K562),human epidermoid carcinoma(KB), murine sarcoma 80 (S-180) and normal human hepatocyte LO_2.By comparing Tf-PEG-Protein conjugates with only PEG-Protein conjugates, the half-life was found to increase by 9.83h. The selectivity of TF conjugates reported the delayed blood clearance and enhanced the active targeting [108].

The poly (ethylene glycol)-camptothecin conjugates (PEG-CPT) to study their anti-tumour effect in the nude mouse model of human colon xenografts. The results showed the passive–tumour targeting of drug, improved biodistribution and drug stability during circulation are made possible using the PEG-CPT. By comparing this with the native drug, the conjugate shows better uptake by the targeted tumour cells, enhanced apoptosis, antitumor stability of camptothecin and the reduced side effect was noticed in the normal cells [109].

5.6.3. Polyglycolic acid (PGA):

Polyglycolic acids are obtained by means of polymerization of glycolic acid units. It is the first biodegradable polymers used in the field of medicine as the absorbable sutures, bone grafts, dental materials and drug delivery vehicles. Dexon is the first biodegradable suture made from PGA, and approved by FDA for its use in medicine.

As the PGA has the high degradation rate, it is easily degraded and excreted out through urine. In order to avoid this PGA scaffolds are not used separately to deliver drugs [110]. Hence, the researchers combined PGA composites with other materials and make them effective, so that it can be used to repair the defects.

The collagen/PGA scaffold was used in the regeneration of rabbit skull defects. The results revealed the development of fibrous connective tissue after 12 weeks of treatment [111].

5.6.4. Polylactic acid (PLA):

Polylactic acids are obtained by means of the polymerization of lactic acid. It consists of lactic acid monomers as its polymeric backbone. The PLA is obtained from the natural feed stocks (wheat, corn and rice). PLA is also a FDA approved drug because its degradation products are non-toxic to the environment. FDA approved the use of PLA along with the direct contact with the body fluids.

Polylactic acid nanoparticles are used as the drug delivery system for hair follicle and sebaceous gland targeting. The PLA particles were loaded with fluorescent drug as a carrier for trans epidermal drug delivery. The penetration activity of the dye from the nanoparticles were investigated in the human skin using microscopic studies.50% of the PLA particles were penetrated into the villus hair follicles by reaching maximum depth corresponding to the entry of sebaceous gland is 12 %-15% in all observed particles. The particle enters along with the dye to the epidermis and sebaceous glands and retain there for 24hrs. The kinetic studies in the skin explants revealed the destabilization of the particles and the release of the dye occurred when comes in contact with the organic solvents and the skin surface. Hence, this investigation shows that the PLA acts as the drug delivery system [112].

5.6.5. Poly (D, L-lactide-co-glycolic) acid (PLGA) PLGA:

PLGA is a copolymer of PLA and PGA. This polymer is made up of two different monomers (lactate and glycol ate). PLGA is prepared by catalyst-mediated random ring opening copolymerization of lactic and glycolic acid and linked by ester linkage. It is a FDA approved synthetic polymer which is directly used to formulate the nanoparticles to the site along with the drug. These polymers are used for various cancer therapies.

The mPEG-PLGA oxaliplatin-loaded (ICD promoters) nanoparticles showed high response in the mouse with pancreatic cancer. PLGA-NPs are loaded with chemotherapeutic agent (gemcitabine) are used as the control with low effectively. The cells are used as the

vaccines for the generation of effective and adaptive immune response in well established in cancer immunotherapy [113].

Cancer cell membrane-coated PLGA nanoparticles were prepared and the dual modal imaging-guided photo thermal malignancy treatments were performed .The core was made near the IR light absorbing agent. PLGA NPs were loaded into ICG (indocyanine green) and their surfaces were coated with cancer cell wall by extrusion of cell membranes vesicles and ICG containing PLGA-NPs through polycarbonate membrane with 220nm in diameter nanoparticles. As a result the positive thermal effects were notice in ICG-loaded cancer cell membrane coated with PLGA-NPs. They respond similarly in terms of cell model and animal testing to see the targeting effects. ICG Nps showed significant accumulation in subcutaneous breast cancer tissues in tumour cell of (MCF-7)mice with target specificity and EPR effect. Hence, it establishes the usefulness as the agent to exactly locate the tumour location [114].

6. Conclusion:

Current usage of the nanoparticles in the field of medicine mainly for targeted drug delivery was discussed in this paper. The information regarding types of nanoparticles and their applications in drug delivery were collected and quoted in this paper.

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