

Utilization of Polymeric Nanoparticle in Cancer Treatment: A Review

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Abstract

Rapid advancement in medicine and biotechnology has driven the field of drug discovery. Novel approaches of drug delivery such as formulating the polymeric nanoparticles is revolutionizing the future of medicines. Newly potent and target specific drugs led to enhance therapeutic utility. These challenges, coupled with the complexity and variety, are fueling the advancement of novel drug delivery systems that overcome bioavailability and delivery obstacles. In present scenario, nanoparticles have been acting as carriers for delivering a wide range of potential drugs. Due to their versatility and wide range of properties and they represent a promising drug delivery system of controlled and targeted release. The utilization of polymeric nanoparticles is a plan that aims to minimize adverse effect and will optimize therapeutic effects. Nanoparticle-based therapy facilitates safe and efficacious therapy for cancer patients. Advancement in Nanomedicine technologies provides clear evidence that polymeric nanotherapies have a significant impact in oncology. Improvement in therapeutic utility of polymeric nano-particulate system is highlighted in this paper. This review deals with the polymeric nanoparticulate systems, fate of nanoparticles, its types, targeting mechanism, application and recent patents.

Keywords: Polymeric nanoparticle; Drug delivery; Cancer; Targeted drug delivery; Oncology

Introduction

Nanoparticle is a term may be defined as a particle having either one or more dimensions of the order of 1000 nm size or less. Nanoparticles novel properties can be differed significantly from bulk materials generally formulated of a size of 100 nm [1]. Cancer is a group of diseases which involves uncontrollable and abnormal growth by means of the potential to invade or spread to other parts of the body. Due to lack of target specificity and advocating high toxic adverse effect, chemotherapy is less opted for cancer treatment. Nanotechnology has greatly revolutionized the therapy of cancer. It minimizes the current limitations in conventional therapy. Thus, nanoparticle increases the target specificity and therapeutic utility of drug [2]. Passive and ligand based targeting mechanism, nanoparticles directly target to the tumor site for treatment. Nanomedicines include polymeric nanoparticles, dendrimers, polymer molecules, polymersomes, polyplexes, and polymer-drug/protein conjugates. This will result in the improvement of cancer therapeutics. The broad scope for chemically modifying polymer has versatility in delivering system. In the field of the scientific research, nanotechnology mainly including the magnetic, materials development and biomedicine, optics, information technology. Nanomedicine has a wide application provides fundamental benefits in nanotechnology [1,2]. These are generally applicable where devices such as nanomachines, nanofibers, nanoparticles, mechanical and optical nanosensors [3]. This review focuses on polymer-based targeted nanocarriers considering therapeutic aspects in the field of oncology. Cancer nanotherapeutics is being implemented in new era moving ahead abating all the demerits of conventional drugs. Nanoparticles have been intended for optimal surface characteristics and particle size. By this, improvement in the distribution of cancer drugs and increasing circulation time in

bloodstream observed. Nanocarriers have been acting as a carrier for loading active drugs for targeting tumor cells. Nanocarriers selectively use the exclusive pathophysiology of cancerous cell by enhancing their retention effect, permeability and the tumor microenvironment. Active targeting strategies utilize legends or antibodies against selected tumor targets amplifying the specificity. Toxicity and Drug resistance are the main problem that impedes the efficacy of both conventional chemotherapeutic and molecularly targeted agents. So, nanoparticles might overcome and reduces the obstacles in treatment of cancer. The ability of Nanoparticles being accumulates in cells without recognizing by P-glycoprotein. It results in increased intracellular concentration of drugs. Multiplex and multifunctional nanoparticles are now being dynamically investigated. It also preferred as the next generation of nanoparticles, modifying cancer treatment techniques [4]. The colloidal particles which are of size in between 10-1000 nm are termed as nanoparticles. To provide efficient therapy nanoparticles are utilized. Following are the novel properties of polymeric nanoparticles- Its small size; High surface area to volume ratio; improved chemical; physical and biological properties; deep entrance to cells and organelles [5].

Rationale of Nanoparticle Drug Delivery System

The rationale of using nanoparticles for tumor targeting is to provide delivering the dose of the drug within the locality of the cancerous cell specifically, Enhancing permeability and retention effect or active targeting improves nanoparticle efficacy, nanoparticles also have ability to reduce the drug exposure to healthy tissues by restricting distribution of the drug to the target organ [6].

Advantages of polymeric nanoparticles

Advantages include targeted drug delivery, its preparation is fairly easy, polymeric nanoparticles have good control over size and size distribution, it has the best protection ability of encapsulated drug

from climatic factors, it has good retention of drug at the active site, it takes a long time to clear out from the body. It has a high therapeutic efficiency. Nanoparticles have better bioavailability. Dose proportionality is less variant than conventional, it has less toxicity, and larger surface area facilitates faster dissolution of active agents in an aqueous environment. It has also greater dissolution which generally equates with greater bioavailability. Its variability effect is minimized.

Disadvantages of nanoparticles

Demerits comprises of limited targeting abilities. Toxicity observed due to excess use of a detergent-polyvinyl alcohol. Discontinuation of this therapy is not possible. Autonomic imbalance disturbance can be occurring through polymeric nanoparticles. It will exert direct effect on heart and vascular function.

Therapeutic applications of nanoparticles

Nanoparticles with different features, characteristics and composition are investigated for various therapeutic applications. These are as follows: Carriers of drugs and biological agents. It is used as carriers of gene and DNA. It acts as Carriers of antigens and vaccines. It also includes controlled & targeted drug delivery. It has wide application as carriers of diagnostic agent; Carriers of MRI contrast [7].

Selecting a Polymeric Drug Delivery

It should be noted that drug release from any carrier is determined by a composite contact between drug and polymer. Generally, it depends upon the properties of drug and the characteristic features of polymer characteristics, and environmental *in vivo* conditions.

Factors considered in the formulation

There are some factors that should be considered during formulation development:

- a) Drug-drug properties, preferred location of the action, Challenges in delivering pattern, a desired releasing pattern associated with the drug.
- b) Drug loading capacity, type of routes preferred for administrating drugs.
- c) Polymer selection-compatibility with drug, desired release kinetics including degradation rate.

Types of Nanoparticles

On the basis of incorporating materials

Silver: *Azadirachta indica*, *Capsicum annum*, *Carica papaya* are the natural precursor for silver nanoparticles biosynthesis [8,9]. A good antimicrobial activity against eukaryotic micro-organism viruses and bacteria has been observed in silver nanoparticles [10]. Hence, their application as nanomaterials in antimicrobial activity, cosmetology, water treatment, textile industry etc.

Gold: Gold nanoparticles (AuNPs) are utilized for protein interactions in immunochemical studies. They are used in the characterization of amino-glycoside containing antibiotics. These include gentamycin, neomycin and streptomycin [11]. In DNA fingerprinting it has been used as a lab tracer for detecting presence of

DNA in a particular sample. They are also used for Gold nanorods are being used to detect cancer stem cells. Another application involves identification of bacteria and for diagnostic purposes [12].

Alloy: oxides of metals have higher and better electrical conductivity among all other metal materials [13]. Exhibiting structural properties different from the samples in bulk, Alloy nanoparticles have better capability and mostly used [14]. Examples include bimetallic alloy nanoparticles, which are generally influenced by both metals exerts enormous merits over normal metallic NPs [15].

Magnetic: Biocompatible Magnetic nanoparticles like maghemite Fe_2O_3 and Fe_3O_4 (magnetite) have been dynamically investigated for targeted cancer treatment e.g. Magnetic hyperthermia) guided drug delivery, gene therapy, Magnetic Resonance Imaging (MRI), sorting and manipulation of stem cells [16].

On the basis of nanoparticle dosage form

Nanosuspension: A nanosuspension can be defined as a suspension of drug nanoparticles in a liquid, particle size lies in between 200-500 nm. It has excellent characteristic of nanosuspension is its solubility, increased saturation, and increased dissolution rate of compound. Achievement of an increased solubility occurs below a particle size of 1 μm [17]. Being Nanosuspension, there may be chances of changes in the crystalline structure increase the amorphous fraction in particle Nanoparticles and Nanosuspension [18]. It has been observed that to enhance absorption rate and bioavailability nanosuspension is orally administered. More adhesion to the tissues and greater contact time gives the better effectiveness of the drug. The example includes Ibrufen nanosuspension for ocular activity prepared via emulsion-solvent diffusion technique to improve bioavailability.

Solid Lipid Nanoparticles (SLN): The entity composed of the lipid, which is dispersed in a surfactant containing solution or water forms solid lipid nanoparticles are termed as sub-micron colloidal carriers. Its size ranges from 50-1,000 nm. In array to defeat the demerits linked to the liquid state of oil droplets, it has been replaced by a solid lipid nanoparticles [19].

Polymeric nanoparticles: Polymeric nanoparticles are formed by dissolving, entrapped, absorbed, encapsulated drug in nanoparticle matrix. Different properties and release characteristics of nanoparticles for the encapsulated therapeutic agent can be achieved. Vesicular systems of nanoparticles represent drug confined to a cavity surrounded by unique polymer membranes, whereas nanocapsule or nanospheres are systems in which drug is uniformly dispersed mechanically. The Nanoparticles drug delivery system has enormous advantages over other delivery systems like due to their small size, capability to penetrate through smaller capillaries and is easily taken up by cells, which facilitates efficient drug accumulation at the target sites. And another point, biodegradable materials has been used for preparation of nanoparticles. It will allow sustained drug release within the target site over a period of days or even weeks [20].

Polymeric micelles: Polymeric micelles as drug carrier have better thermodynamic stability in physiological solution [21]. Micelles have a fairly narrow size distribution in the nanometer range. They are easily identified through their specific core-shell. Micellar systems are useful for the systemic delivery of water-insoluble drugs [22]. Drugs can be partitioned in the hydrophobic cores of micelles and the outer layer i.e., hydrophilic form dispersion in aqueous media. It is stable and can be administered intravenously. On intravenous administration, polymeric micelles prolongs the time of systemic circulation. Because

of their smaller size and hydrophilic shell, this diminishes their uptake mechanism occurs through reticuloendothelial system. Polymeric micelle-incorporated drugs may accumulate in cancerous cell to a greater extent than free drugs. Further on shows reduced distribution in nontargeted areas.

Magnetic nanoparticles: Magnetic nanoparticles are used as a novel drug carrier system has powerful and versatile analytical tool in the field of medicine industry. The magnetic nanoparticle is prepared by coating with an inorganic core of iron oxide and polymer such as dextran. Magnetic nanoparticles like indomethacin have been reported for targeting under magnetic field of 8000 OE-strength in the delivery system [23].

Carbon nanotubes: Carbon nanotubes are a new form of carbon molecule around in a hexagonal arrangement of carbon atoms. These are hollow cylinders of diameter as small as 0.7nm and reach several millimeters in measurement lengthwise. The small dimensions of nanotubes combined with their extraordinary properties like-physical, mechanical and electrical & make them unique materials. Its mechanical strength is sixty times more than that of the best steels. Carbon nanotubes have greater surface area, are excellent heat conductors and display unique electronic properties, offering three dimensional configurations. They have higher capacity for molecular absorption [24].

Liposomes: Liposomes are small artificial vesicle system of spherical shape formed from natural, non-toxic phospholipids and cholesterol. Due to its size, hydrophobicity, as well as biocompatibility, liposomes are promising system for drug delivery. Liposomes can be utilized as a versatile tool in biochemistry, biology and medicine. Liposomes utilizes as a carrier system for drug delivery have distinctly changes

drug pharmacokinetics properties compared to solution containing drugs. Liposomes show less systemic toxicity and prevent early degradation of the drug after it has already been introduced in target organs shows organ specificity [25].

Nano shells coated with gold: Gold nanoshells can be defined as new composite nanoparticles in which infrared optical activity combined with the uniquely biocompatible properties of gold colloid. Concentric sphere nanoparticles consisting of a dielectric (typically gold sulfide or silica) core and a metal (gold) shell termed as metal nanoshell. Variation in the absolute size of nanoshell can be made to scatter incident light and variation in relative thickness of shell layers and core, the Plasmon-derived optical resonance of gold can be significantly shifted in wavelength from the visible region of highest physiological transmissivity. Gold nanoshells surface properties are almost identical to those of gold colloid because of deposition of gold shell layer by chemical method results in formation of Gold Colloid. Gold nanoshells can be used to treat breast cancer cells through invasive methods [23].

Ceramic nanoparticles: In this new era, ceramic nanoparticles prepared by using entrapped biomolecule using inorganic (ceramic) material. The merits of ceramic nanoparticles over other carrier system are small size, porosity, and resistibility in pH has wide application in industry of modern materials science including drug delivery system [7].

Nanopores: Now days due to its better thermal insulation, release and their applicability as fillers, controllable material separation nanopores are used for catalysis such as aerogel formulated via sol-gel technology. Hence, materials like nanopores of pore-sizes in nanometer have a significant role in industry [26].

S. No.	Type of nanoparticles	Application	References
1	Nanosuspension and Nanocrystal	Provides secure & steady system for prohibited delivery of drug which is poorly soluble candidates	[21,27]
2	Solid lipid Nanoparticles	as colloidal carrier system alternative materials to polymers	[28]
3	Polymeric Nanoparticles	Used in targeted drug delivering system	[29]
4	Polymeric Micelles	For controlled and systemic delivery of water insoluble drugs	[30]
5	Magnetic Nanoparticles	In drug targeting and as diagnostics agents in therapy	[31]
6	Carbon nanotubes	In DNA & Gene delivery controlled release of drug	[32]
7	Liposomes	For Controlled targeted drug delivery	[26]
8	Nanoshells	In tumour targeting	[33]
9	Ceramic Nanoparticles	Used in drug & biomolecule delivery	[34]
10	Nanopores	As a controlled release drug carriers	[35]
11	Nanowires	Facilitates transportation of electrons in nanoelectronics	[36]
12	Quantum dots	As a targeting imaging agent	[37]
13	Nanofilms	Used for systematic or local drug Delivery	[38]
14	Ferrifluids	For capturing cells and other biological targets	[27]

Table 1: Types of nanoparticles.

Nanowires: Nanowires can be defined as semi conductive or conductive particles with a high length/diameter ratio and a crystalline structure of a few dozen nm. Examples-such as silicon, gold, copper, cobalt-based nanowires have already been formulated successfully (Table 1).

Selection criteria for polymeric nanoparticle preparation: The potential five principles for the preparation of safe drug loaded polymeric nanoparticles-Size reduction of the drug in the nano range without changing the utility of medicine. Non-toxic chemicals should be used instead of toxic chemicals in preparation of polymeric nanoparticles; Bonding between atoms and molecules to nanoparticles gives the desired property of drug product and avoid related toxicity; Non-toxic polymers have been selected which have the capability to reduce the toxicity occurred during encapsulation of highly toxic drugs; On using a limited quantity of toxic chemicals to avoid its toxic effects.

Localization of Polymeric Nanoparticle

Targeting mechanism

Passive targeting: Utilization of passive targeting of polymeric nanoparticles in the field of oncology has enhanced. Due to enhanced permeation and retention, an Effect is observed called (EPR) effect. The principle was established on the basis of passive targeting of polymeric nanoparticles to tumor cells [37]. In their early study, extensively more concentrations of the Anticancer drug like neocarzinostatin was discovered. For postal administration, it is subjected in tumor tissue of the polymer-drug conjugate poly (styrene co-Maleic acid) neocarzinostatin (SMANCS). In contrast to control the experiments the drug was administered in its free form. Then Maeda et al., Hypothesize and observed the growth of nanoparticles. Observation includes increased growth of the polymeric nanoparticles in the tumor. It was accredited to the structural features of the tumor vasculature; this effect is known as the EPR effect [36]. A wide range of macromolecular agents such as proteins-immunoglobulin G (IgG), liposomes, micelles has been used. These types of nanoparticles, which can be utilized in showing the EPR effect [38]. EPR effects mainly ground to the designing of nanomedicines for specific cancerous cell targeting. Its application also includes drug delivery or imaging applications. Factors that should be considered for passive targeting of nanoparticle like Surface should be modified. Modification should be done via coating of nanoparticles with a polymer (PEG). The coating is done in favor of biocompatibility & to avoid the endocytic uptake by tumor cells [39]. This problem has been referred as PE dilemma. This dilemma has been recommended for efficient drug delivery for cancer targeting. It also includes passively targeted polymeric nanoparticles. These were released, their therapeutic load into the milieu (tumor) rather than within cancer cell [40]. On delivering high amounts of drugs to cancerous cells leads to exposure for a longer duration and efficacy is also increased. Docetaxel (Dtxl) is an example, whose elimination half-life of 22 h in cancer. Docetaxel have 2.2-4.5 h half-life in normal tissue representing long tumor site retention relative to non-cancerous tissues. Passive targeting refers to the *in vivo* natural distribution pattern of drug carrier system. The mechanical setup of large size microspheres and big polymeric nanoparticles agglomerates (>4 μm). It can occur by capillary blockage which is referred as passive targeting. This process can be exploited to target passively to the lungs. This is targeted via the venous supply or to other organs or the appropriate arterial supply [41].

Active targeting

On directing alteration in natural distribution pattern of a carrier particle to the specific organs or cells termed as “active targeting”. The methods are mainly used such as surface properties alteration done by coating the nanoparticles with surfactants; Incorporation of magnetite particles into the particles and the application of a magnetic field, changes in surface charge, & connectivity of specific antibiotics to the nanoparticle surface. Active tumor targeting of polymeric nanoparticles may be achieved with either direct targeting or the retargeting method. The Direct Targeting comprises of nanoparticles which are mainly coupled with the legend through a covalent bond. The ligand coupled nanoparticles are received by the tumor cells. Expression of a homologous receptor on their surfaces takes place. The specific ligand receptor binding ensures that the nanoparticles carrying drugs will get attached specifically to the tumor cells. It will result in delivery of potent drug specifically in cancerous cells expressing receptor and not the normal healthy cells [42]. Nanoparticle can overcome the gastrointestinal barrier& have the capability to enhance the interaction mechanism of drug delivery [43]. Tumor targeting by drug loaded nanoparticle in normal as well as tumor tissue depicted in Figure 1.

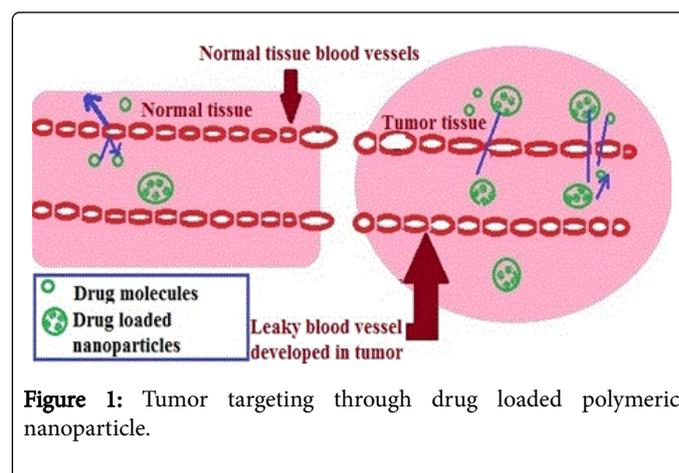


Figure 1: Tumor targeting through drug loaded polymeric nanoparticle.

Biocompatibility of biodegradable polymeric nanoparticles

Currently biocompatible polymeric nano-formulations undergo backbone degradation releases in presence of hydrogen peroxide. There are two polymeric structures which differed in terms of either direct or through linkage in polymeric backbone or linkage between boronic ester chains. In the presence of hydrogen peroxide, polymers were stable in aqueous solutions. Being exposed to the peroxides removal of the boronic ester groups takes place. Groups removed at physiological temperature and phi Phenols group which was along the backbone undergoes polymer degradation through quinine methide rearrangement phenomenon. To study & analyze Oxidation releasing properties, nanoparticles were currently formulated. These polymers provide a biocompatibility, biologically relevant, and novel approach. These kind of system termed as H_2O_2 -triggered biodegradable release systems. It can easily release and degraded into smaller molecules after sometimes clearance occurs through bodies [44]. Extent of biocompatibility depends upon the interaction ability of nanoparticles with the body. Nanoparticles should not produce toxicity, thrombogenic, carcinogenic and immunogenic responses. Relevant factors should be considered in biocompatibility evaluation. Firstly, anatomically reliability of nanoparticle should be concerned. The

immunological reaction varies from location to location. For example, polymer based such as poly (lactic-co-glycolic acid) and polymeric microspheres makes mild tissue associated reactions. These were finely characterized, whereas acute inflammation occurs due to production of the same particles in connective tissues surrounded by nerves [45]. Secondly, Intrinsic characteristics of batteries should also be considered whether that nanomaterial were biocompatible or not. There is the advantage of using PLGA nanoparticles over PLGA microparticles as they have rapid clearance. They also do not cause adhesion on peritoneal cavity over long periods of time [46,47]. The immune response study represents immunocompatibility to medical devices, prosthesis, and biomaterial drawn chief vicinity of concern. Factors like the accumulation of particles, immune system alteration, blood component interactions, & organ clearance should not be ignored. Nanoparticles have property to either suppress or stimulate immune response. Nanoparticles also may optimistically or negatively affects the particle function in various applications. Interaction of nanoparticles with blood depends upon surface properties of nanoparticles. Immunological reactions take place in the bloodstream leads to make drug nanoparticles inactive. It has been reported that nanoparticles, which lacks surface modifying properties induces macrophages effects. It also clears out nanoparticles from the blood stream for prevention of opsonins adsorption [48]. Biocompatibility studies of polymeric nanoparticles include preclinical examination. This examination includes such as leukocyte proliferation, macrophage uptake, platelet aggregation, complement activation, haemolysis, and coagulation [49].

Cellular uptake of polymeric nanoparticles

Characterization and Cellular uptake of nanoparticles is important to understand through NP scan which helps to deliver drugs into the

cell. Cellular uptake of polymeric nanoparticles can be described by concerning factors such as material, electric charge, shape, size, surface properties. Due to degradability of nanoparticles, it is difficult to study kinetics of cellular uptake of nanoparticles in the body. Spring 2013 thesis stated that cellular uptake would be high due to contact mediated cellular uptake of putrescent, a dye leaked via nanoparticles [50]. In recent paper two cell lines were taken from experiment. During experiment, it has been observed that on modifying surface properties and particle size reaction of both cell lines are differing with each other. The images depicted in paper reveal that a cell absorbs free dye during experiment. Poloxamer 188 & Polysorbate 80 used as surfactant to enhance cellular uptake of polymeric nanoparticles [51,52]. Small molecules have tendency to penetrate into cell membrane compartment easily as their size is small. Diverse mechanism applicable for nutrients uptake between or among the cellular region occurs in plasma containing membrane. Nonpolar molecule, CO₂, O₂ are diffuses into membrane. Ions and some aminoacids are transported through active transport mechanism of ion channel and protein pumps [53]. Hydrophilic biomacromolecules are transported through endocytosis. Endocytosis is a pathway which facilitates vesicles transport via plasma membrane [54]. Biodistribution and cellular uptake of polymeric nanoparticles depends upon surface characteristics, physical and chemical properties. Nano-immune interactions should be considered as recognition of particles and engulfing phenomenon occurs through immune cells takes place. Primary cells are significantly used for testing biocompatibility of the nanoparticles. As primary cells are nearer to *in vivo* conditions compared to tr-cell lines (Table 2) [52,55-60].

S. No.	Uptake pathways	Description	References
1	Caveolae dependent endocytosis	Caveolae, small-flask shape pits present in membrane, consisting of binding protein caveol bonded with cholesterol (200-500 nm)	[60]
2	Clathrin-mediated endocytosis	Clathrin-coated vesicles containing plasma membrane protein with receptor sites specific to the nanoparticles being internalized [100-150]	[61]
3	Pinocytosis macropinocytosis	Cell drinking, non-specific, 0.5-5 µm in diameter for macropinocytosis	[62]
4	Phagocytosis	Internalization of whole neutrophils, large particles, macrophagocyte	[63]

Table 2: The main pathways for cellular uptake.

Pharmacokinetic and biodistribution of polymeric nanoparticles

It was reported that nanoparticles represents their role in improving effectiveness of drug having low bioavailability and low therapeutic window (nucleic acid drugs and antitumourol drugs) has been used exclusively. The biodistribution as well as pharmacokinetics parameters define their therapeutic utility and side-effects. Factors such as physical and chemical factors included in chemistry of surface-charge. These factors were utilized in the determination of biodistribution extent and pharmacokinetic parameters. After internalization of cells, nanoparticles intracellular fate prominently affects bioavailability. For overcoming the barriers in intracellular delivery and releasing pattern of drug has been implemented for better drug delivery systems [61]. Neovascularization is the fast growing cancerous cells requires blood

vessels which provide nutrition and oxygen for their existence [62]. This leads to formation of abnormal structures like fenestrated endothelial which surrounds the cancerous cells [63]. The optimum size of nanoparticles avoids renal elimination & MPS and entering through EPR. Further, size of nanoparticles and range of pore may vary in species as well as type of tumors. In extracellular spaces region, nanoparticles of size more than 100 nm get easily trapped. There by it cannot penetrate from leaky vessels during extravasation [64,65]. However, under hydraulic pressure, nanoparticles less than 20 nm have deep penetrability into region called perivascular area of tumour cell [64,66].

Biodegradability of polymeric nanoparticles

Encapsulating the drugs into nanoparticles provide effective cancer therapy. Hydrophobic drugs having less solubility in the water can be delivered through nanoparticles. Target specificity of drug in cancerous cells can be achieved by either active or passive targeting mechanism. The thesis concluded that development of multimodal polymeric nanoparticles. In which nanoparticles explores cellular or intracellular uptake and degradation phenomenon at Paper of SINTEF. Drug delivery system also develops and evaluated two kinds of nanoparticles. These were fluorescent imaging nanoparticle & confocal laser scanning microscopy. Confocal laser technique along with flow cytometry utilizes for characterizing the biodegradation and cellular uptake. While fluorescent imaging provides characterization of degradation intracellular region. Cellular uptake and degradation mainly dependent upon maturation of cells and cell confluency. Caveolin & Clathrin mediated mechanism involved in uptake tends to provide biodegradation. It was reported as Polyoctyl-cyanoacrylates has less promising candidate for drug delivery. As it do not degraded easily in first week. Another example comprises -Poly-butyl-acrylates degraded within 24 h through Clathrin-mediated-endocytosis uptake. These particles can be useful in imaging or controlled drug delivery systems. Hence, it has been declared that nanoparticles were easily degraded within cytosol which is efficient for delivering systems [55].

Biodegradation Factors: It involves various factors involves: a) Morphological factors such as size and shape. b) Chemical factors involves composition, molecular weight, chemical structure, presence of ligands, presence of ionic groups and its configuration structures, and c) Physical factors like variation in diffusion coefficient [56].

Cytotoxicity and elimination of polymeric nanoparticles

Biological consequences should also be concerned. It is done to access Cytotoxicity and elimination patterns of polymeric nanoparticles after translocation, cellular uptake, and intracellular location process. Cytotoxicity becomes most critical aspect associated with biomedical utilization of polymeric nanoparticles. Improved characterization data of Nano formulations has been utilized in designing future experiments to study nanotoxicity. Nanotoxicity studies include chemicals adsorption over surface of polymeric nanoparticles & occurrence of Interaction phenomenon within the cell [61].

Cell recognition and functionalization of nanoparticles

Cationic coating was utilized as functionalized nanoparticles. In live cells, functionalized nanoparticles were introduced without doing any kind of endocytic internalization modification. Internalization phenomenon was considered as non-selective as it depends upon particle adsorption over surface of cell. For cell recognition, availability of a coumarin and nanoparticles [$d=2.6$] and its conjugates with the folic acid is necessary. It can be recognized by receptors found on the surface of cell known as folate receptor. Functionalization includes coumarine as well as folic acid present over by Fourier transform infrared spectroscopy. After incubation of KB cells termed as Pharyngeal cell from human body. It has been observed that Cellular recognition of polymeric nanoparticles occurs which leads to facilitate specific cell delivery system [67].

Types of functionalization of polymeric nanoparticles

1. Functionalization through ligands: Sensing of biomolecule can be achieved via incorporating ligands over surface of nanoparticles [68]. Disease diagnosis, intracellular delivery, diagnostic purposes can be done through ligands incorporation method [69,70]. Differential affinity has also been observed towards cell surfaces and proteins employing their identification [71]. Distinguishing between cancerous and healthy cells can be done through a protein known as green fluorescent protein [72]. Replacing GFP (green fluorescent protein) by gold nanoparticles restores fluorescence in GFP which provides sensing property. Slight change in head groups of ligands tends to enhance cell affinity of nanoparticles. Surface charge in combination with aromatic stacking & hydrophobicity leads to play very important function in application of sensing purposes. Functionalization of polymeric nanoparticle through ligands can be depicted in Figure 2.

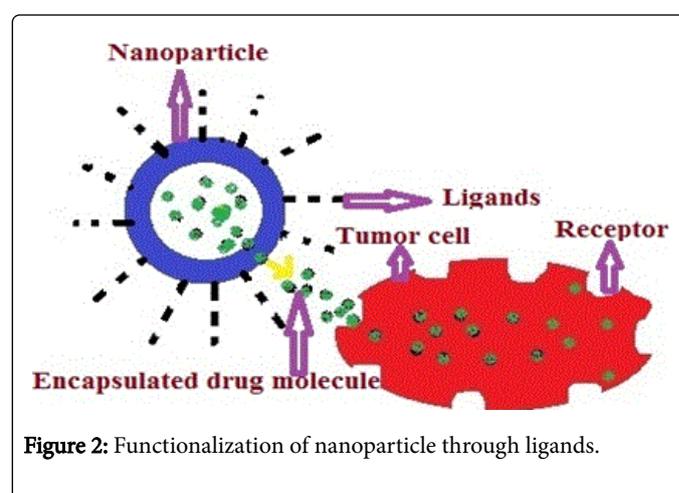


Figure 2: Functionalization of nanoparticle through ligands.

2. Polymer functionalized nanoparticles: An alternative approach comprises of ligand molecule coated with polymers. Coating provides macromolecular properties system to the surface of nanoparticles. Nanoparticles can be coated with the polymer such as PEG which exerts EPR effect. It mainly concern with effective targeting of tumour cell through passive targeting mechanism [73]. Polymer coating provides enhanced particle in cancerous cells, increased time of circulation. It also prevents blood serum proteins to adsorb [55,56]. PEGylated polymeric nanoparticles attached with targeted moieties have greater affinity in targeting of cancerous cells [74]. PEGylation enhances the stabilization of salt in solution as compared to unchanged nanoparticles. Accumulation of transferring content observed *in vivo* around solid tumour cell [69].

3. Biomolecule functionalized nanoparticles: Efficient biomacromolecules delivery with negligible Cytotoxicity provided by biomolecule functionalized nanoparticles in which nanoparticles are coated with biomolecule [75]. Example such as Oligonucleotide-AuNP with gold thiol leads to formation of bond between them reported by alivisatos and mirkin [76,77]. Scavenger receptors mediate the uptake phenomenon of anionic nanomaterials [78].

Fluorescent nanoparticles

Recent developments provides platform for treatment and diagnosis purposes in nanotechnology. Fluorescent polymeric nanoparticles act as efficient tool at for diagnostic purposes in oncology therapy. Fluorescents nanoparticles such as quantum dots, up conversion

nanoparticles, organic-dye-doped nanoparticles have great application in characterization purposes. At animal level, fluorescent nanoparticle is optical imaging technique. Optical imaging is highly sensitive useful in characterization of cancerous cells in cellular region. In this technique; Conjugation ability of the functional molecule forms conjugates with nanoparticles having multi-functional attributes. Functional biomolecule such as, imaging probes, targeting moieties, therapeutic agents give advancement in diagnostic & clinical therapies. It has greater utility in oncology area utilizing fluorescent nanoparticles in *in vivo* as well as *in vitro* imaging purposes. Light photons can be detected which is transmitted through various tissues is done by optical imaging technique. In cancer therapy, non-invasively optical imaging techniques were utilized in monitoring extent of disease. Initially, Bioluminescent proteins, fluorescent proteins, fluorescent dyes act as conventional fluorophores. Development & formulation of fluorescent nanoparticles leads to form potential candidates used for imaging purposes [47]. For example:

a) Organic dye-doped nanoparticles: Recently, Organic dyes have been incorporated with polymeric nanoparticles for characterization and imaging purposes. Stability can be achieved by nanoencapsulation of organic dye which tends to amplify the signal significantly. Now Nanoparticles like PLGA or silica nanoparticles have been dipped in organic dyes (e.g. (FITC) Fluorescein isothio-cyanate, IRG-023 Cy5, RITC (rhodamine B isothio-cyanate) etc. [49]. Nanoparticles labelling have also been demonstrated [79].

b) Quantum dots: Semiconductor crystals of size ranges in nanometer are termed as quantum dots. Composition of these quantum dots are taken from periodic table groups III to IV, II to VI and IV to VI. Quantum dots size ranges from 2 to 10 nm. Being small in size they have better quantum confinement effect. Absorption spectrum of quantum dots is broad and quantum dots have narrow emission spectrum. Its applicability observed at wide range of wavelength. Multiple labels associated with Cellular imaging are done through excitation of single excitation of quantum dots. Due to their greater tunability, emission wavelength can be controlled via size of quantum dots.

c) Up conversion nanoparticles (UCNs): In near infrared region, phosphores absorbs light and emitted in visible region, this phenomenon exhibited by up conversion nanoparticles. Host lattices such as LaF₃, Y₂O₃, NaYF₄ co-doped with Yb³⁺, Tm³⁺ (trivalent earth ions) are useful in up conversion nanoparticles formation [80,81]. Up conversion nanoparticles crystals doped in lanthanides groups can also be act as emitter as well as absorber. In recent years, it has been seen

that up conversion nanoparticles achieved enormous popularity. These nanoparticles have wide biological application such as photodynamic therapy [80], studies by FRET, immunoassay [82], in microarray [83], detection of DNA at clinical stage.

Carrier for polymeric nanoparticles: polymers

The ideal polymeric carrier criteria for nanoparticles are: biocompatibility, biodegradability. It can be easily synthesize and characterize. Economically, it is Inexpensive, non-immunogenic, Water-soluble & Non-toxic in nature. The polymers used for preparation of nanoparticles are as follows: i) Natural hydrophilic polymer, and ii) Synthetic hydrophobic polymer.

Natural hydrophilic polymer: These include polysaccharides (dextran, alginate, chitosan, agarose) and proteins (albumin, gelatin, legumin, lecithin, and vicillin) and polysaccharides (alginate, dextran, chitosan, agarose and pullulan) are commonly used. But due to their poor reproductively batch to batch variation, these polymers get easily prone for potential antigenicity and degradation.

Synthetic hydrophobic polymer: These can be sub-divided into following two groups:

i) Polyesters such as (poly (caprolactone), poly (lactic acid), poly (lactide-co-glycolide).

ii) Poly-alkyl cyanoacrylates, (poly (isobutyl cyanoacrylates), poly (butylcyanoacrylates), poly methyl (methcyanoacrylates) [84]. Polymeric nanoparticles have been prepared by using following polymers nanoparticles are given as follows: Natural polymers; Synthetic polymers.

Natural polymers: Natural hydrophilic polymers such as proteins (albumin, gelatine, legumin or vicillin) and polysaccharides (alginate, dextran, chitosan, agarose, pullulan). But these natural polymers have some disadvantages such batch-to-batch variation, conditional biodegradability, and antigenicity [85-88].

Synthetic polymers: The synthetic polymers are divided into following two groups:

a) Pre-polymerized: Poly (lactic acid), Polystyrene, Poly (ε-caprolactone) (PECL), and Poly (lactide-coglycolide) (PLGA) etc.

B) Polymerized in process: Poly methyl derivatives like (methacrylates); Poly (isobutylcyano acrylates) (PICA), Poly-butylcyanoacrylates (PBCA), and Copolymer e.g. Amino-alkylmethacrylate methyl methacrylate (Tables 3 and 4) [23].

S. No.	Inventor name	Work done	References
1	M. Davis	Dynamic charge state cationic polymer	[89]
2	K. Krishna	Composition, Methods for expandable microsphere	[90]
3	H. Yaoliang	Expandable Microsphere	[91]
4	L.L. Lian	Compilation of Polymer & Medical Devices	[92]
5	B. Xavier	Cosmetic composition as keratin material	[93]
6	B. Marcia	Embolic Polymer Particle	[94]
7	E.Z. Stephen	Therapeutic Nanoparticles	[95]

8	Tseitlin	Description about binder composition	[96]
9	Y.D. Igor	Nanocomposite preparation	[97]
10	H. Munir	Zilicon nanoparticles composite as U.V absorber	[98]
11	A. Eschborn	Movement Device for Nanoparticle Dispersed Polymer Matrix	[99]
12	M. Shlomo	Polymer having chelating agent	[100]
13	S. Freedy	Formulation for breast prosthesis disorder	[101]
14	S. Dazhi	Investigate nanocomposite & nanoplatets	[102]
15	L. Fugang	Formulated Agricultural acting composed & Polymer Form Nanoparticle	[103]
16	L. Jin-gyu	Investigate Proton conducting group	[104]
17	W. Xiaorang	Controlled architecture for nanoellipsoid etc.	[105]
18	V. Alexander	Polymerization Techniques for Vinyl Polymer	[106]
19	P.C. Jean	Studied Shear gelling and shear thickening properties	[107]
20	M. Edith	Investigated bioactive microsphere	[108]

Table 3: Patents polymeric nanoparticles formulations.

S. No.	Patent no.	Formulation title	Nanocarriers	References
1	CN102697737A	Tumour-targeting drug loaded particles	Gelatin & PLGA	[109]
2	CN102525936A	PLGA nanoparticle and preparation method	PLGA	[110]
3	WO2012103634A1	Cellulose based nanoparticle	CMC-AcPEG	[111]
4	CN102793671A	her-EGF modified cisplatin-loaded polymeric nanoparticle, method and application	mPEG PLGA-PLL29	[112]
5	EP2309990B1	Drug loaded polymeric nanoparticles & methods	PLA-PEG	[113]
6	US2012019582A1	Injectable Biomaterials	HPMA-HMA	[114]
7	WO2013127949A1	Functional PLA-PEG copolymers preparation & use	PLA-PEG	[115]
8	US20130209566A1	Nanoparticle composition & methods to make and use	POE	[116]
9	KR1020100037494	Contrast media for cancer diagnosis	HA	[117]
10	CN102697795A	Anti-tumor combined medicament	PLGA	[118]

Table 4: Recent patented polymer based polymeric nanoparticle for cancer treatment.

Application of polymeric nanoparticles

1. **Targeted drug delivery:** A drug entering the body controlled via drug targeting systems. In 20th centuries Paul Enrllich proposed “magic bullet” in which drug has been directly targeted to the desired site of action. To deliver the drug in the right place at the right time can be offered by Nanotechnology techniques. In the next few years, nanotechnology has great impact on nutraceuticals, lifesciences, diagnostic, production of biomaterials etc. Targeting drug delivery is a technique through which the drug-loaded system can directly act to the site of interest [115].

2. **Gold nanoparticles detect cancer:** Gold nanoparticles utilize as ultrasensitive fluorescent probes. This will helpful in detection of cancer biomarkers in blood reported by Chinese scientist. The

approach is employed in detection of viral or bacterial DNA. Gold nanoparticle shows potential probes for biomedical applications. The advantages of gold nanoparticles is that it can be easily prepared unlike other fluorescent probes like organic dyes or quantum dots, as they won't burn out during light exposure [119-122]. In Current era, two essential biomarkers are found i.e., Alpha Foetal protein & Carcinoembryonic antigen. These are mainly investigated to perform diagnosis purposes for various kind of cancer such as lung, breast, liver cancer; this concept was applied by Jicun Ren at Shanghai Jiaotong University in china. The researchers conjugated antibodies with their gold nanoparticles to measure the level of biomarkers [116].

3. **Targeting of nanoparticles to epithelial cells in the GI tract using ligands:** Targeting of nanoparticles improves interaction between adsorptive enterocytes with nanoparticles utilizing ligands. M cells and

enterocytes, glycoprotein & lectin containing ligand site selectively bind through receptor-mediated mechanism. Lectins such as tomato, bean lectin considered to improve adsorption of oral peptide [61]. Under the influence of physiological conditions, absorption of vitamin B-12 occurs mediated through endocytosis mechanism. To enhance bioavailability of colony of granulocyte and erythrocyte stimulating factor binds with vit-B12 bonded through covalent bond has been observed [123,124].

4. Nanoparticles target ovarian cancer: A journal of Cancer Research reported that a gene which produces the diphtheria toxin, responsible for killing cells by disturbing their ability to manufacture proteins. Bacterium *Corynebacterium diphtheria* is a toxin which is widely used. Currently the functional DNA has delivered by polymer-DNA nanoparticle when subjected near or into the targeted tissue/organs. These nanoparticles as an alternative to viruses have been developed by MIT-Lankenau, which are which are coupled with safety risks. In spite of treating ovarian cancer, these nanoparticles have also been established potential for treating various kinds of diseases such as viral infection and prostate cancer [117].

5. Nanoparticles role in blood-brain barrier: Blood brain barrier is a barrier found between central nervous system and blood streamline. In order to maintain passage of nutrients & osmotic pressure, ion exchange takes place across BBB. BBB also protects spinal axis and brain from any kind of bacteriological threats. Drugs which have less hydrophobic character face difficulty in blood brain barrier. Hence, it is impossible for drugs invade through barrier. Entrapping drug within nanoparticles is the way through which delivering of drug to brain/CNS system. Being small in size, penetrability of vascular endothelium has been enhanced. Various studies have showed that drug loaded polymeric nanoparticles used in tumour therapy [118].

7. Stem cell therapy: A new research insights suggest that the nanoparticles are valuable tools for improving stem cell therapy. Nanoparticles have been efficiently utilize by chemical engineers to minimize the muscle degradation and enhances ability of stem cells to regenerate damaged vascular tissues in mice. This study report is published online in Proceedings of the National Academy of Sciences on October 5. Researchers focus on the stem cells role in producing new blood vessels. Cells may not continue to renew tissue effectively with the help of performance-enhancing genes, which tends to promote growth in the target site. In market, some nanotech goods such as films of anti-microbial are available along with improved therapeutic effect. Researchers have shown that viral vectors used to deliver therapeutic genes to stem cells. A variety of other companies are also pioneering developments in packaging of food goods, techniques involved in ensuring food safety supply chain tracking.

8. Diagnostic purposes: Now days Copper chlorophyll nanoparticles are utilized for diagnostic purposes as demonstrated by Yang et al. [123]. These is directly utilizes *in vivo* which can be characterized by (AEM) analytical electron microscopy. In brain, Polysorbate-T 80 coated over nanoparticles has been detected mainly used in determining existence of transcytosis & endocytosis [124].

9. Nanoparticles and targeted drug delivery: The utmost impact of nanotechnologies approaches in cancer therapy is in targeting drug specificity. Efficient delivering of nanoparticles to their biological targets through appropriate application of nanotechnologies leads to improvement in therapeutic index of almost all drugs. Many drugs in case of brain tumor, as won't cross BBB (Blood-Brain-Barrier). Drug-

loaded polymeric nanoparticles are capable to penetrate and cross this barrier, and have been significantly shown too greatly increase therapeutic concentration of anticancer drugs in brain tumors gives better drug targeting. Particle size plays an critical role ensuring the efficiency of drug delivery to various parts of the body. This nanostructure-mediated drug delivery technology were usually applied for realization of nanomedicine & has the efficient potential to improve timed release of drug molecules as well as potential to enhance drug bioavailability enable precisized drug targeting. On using nanoscale drug carriers extra profit have been observed results in more efficient drug distribution and drug toxicity also reduced. Anatomic features such as the blood-brain barrier, the branching pulmonary pathways & tight junction of epithelial layer of the skin make it difficult for drugs to reach specific physiological targets. Nano-drug carrier helps to penetrate or overcome these barriers to drug delivery. Delivery into the pulmonary system is achieved only through particles having diameter <100 nm. Greater uptake efficiency has also been shown with size of 100 and 50 nm for gastrointestinal absorption and transcutaneous permeation respectively. However, additional shedding will allows the release of encapsulate drug for exerting effect. Being biodegradable in nature, gelatin and serum act as promising drug carriers for pulmonary drug delivery system [119].

10. Vaccines and gene therapy: In gene therapy, genes were encapsulated inside the nanoparticles; it becomes necessity to provide protection against degradation under the influence of enzymes e.g. proteolytic enzymes, pH and bile. Stability of genes inside nanoparticles can be ensured through binding of genes to the nanoparticles surface which tends to improve bioavailability and biocompatibility of drug. Surfactants are generally not used in this process, because nanoparticles have capability to binds with DNA i.e., why surfactant is not that much necessary [120]. A potential method has discovered i.e., vaccine therapy for treating Parkinson disease. Delivering of gene in tyrosine hydroxylase shows greater results [121]. Retrovirus or recombining adenoviruses has been used as viral vectors. A polymer like (PEI) polyethyleneimine mostly utilized in entrapment of genes within nanoparticles is most efficient method in gene therapy [122]. These polymers protect DNA within polymeric based nanoparticles. Membrane penetration was favored by binding affinity of heparin sulfate which is expressed on the surface of cell.

11. Anticancer therapies: Due to non-specific bioavailability of anticancerous drug, polymeric nanoparticles are being used currently in anticancer therapies. Bioaccumulation around cancer cells occurs due to EPR effect which leads to exert efficient effect of drug to the target tissues. Hapca et al. prepares PLA nanoparticles in which monoclonal antibodies are grafted. Monoclonal antibodies have great utility in lymphomas and ovarian cancer. Controlled release of HO-1, heme oxygenase inhibitors delivered via nanoparticles carrier [124]. In small quantity Bilirubin is helpful in preventing oxidation of cells. Hence, drug loaded nanoparticles utilizes for anticancer therapies.

Future of polymeric nanoparticle: opportunities and challenges

Nanoformulations like polymeric nanoparticles have already been used as drug carrier in delivering system with great success in oncology. In spite of potential for anti-tumor therapy, It has been also utilizes in gene therapy, radiation therapy, AIDS therapy. It has still greater capability to deliver various proteins, vaccines, virostatics, and antibiotics. It also acts as vesicles to cross blood-brain-barrier in CNS

therapy. Therefore, polymeric nanoparticles provides platform for diverse array of biological applications in future.

Conclusion

This review concludes that polymeric nanoparticle is act as nanocarriers important for treating cancer in oncology. Polymeric nanoparticle has tremendous therapeutic potential at both clinical as well as preclinical development stages. Polymeric nanoparticles have significant role in nano-technology. It has been widely used as carrier for delivering anti-cancer drugs in cancer treatment. Targeted system has proven their efficacy in oncology. Safety of polymeric nanoparticles as nanocarriers is an important factor to be considered while designing of drug. The field of oncology has also been increasing day by day, i.e., why polymeric nanoparticles occupy their place in this field for targeting therapy of cancer. Polymers are currently being used and their properties are modulated to achieve release-control ability and high therapeutic load with resulting strong implication in cancer treatment.

Conflict of Interests

The authors have declared that they have no conflict of interest.

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