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REVIEW ARTICLE

Polymeric Nanoparticles: New Approaches towards Targeted Cancer Therapy with Biomedical Applications

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ABSTRACT

Nanotechnology is a dynamic field and new products containing nanoparticles are being marketed every week. Encapsulation of therapeutic drugs inside nanoparticles has become the new norm in the field of drug delivery. Nanoparticles increase the therapeutic efficacy of the drugs by providing high loading efficiencies, shielding when in circulation, ability to target tumors, enhanced accumulations, and triggered release inside tumors. Polymeric nanoparticles have seen an unprecedented growth and usage in drug delivery and diagnostics in recent decades, and have emerged as extremely promising candidates for targeted delivery owing to their tunable properties, and the flexibility to design systems which respond to external stimuli such as pH, hyperthermia, redox, ultrasound, and magnetic field. This review summarizes recent exciting developments in the field of targeted polymeric nanoparticles for delivery of anti-cancer drugs, with a particular focus on functionalization with ligands, stimuli responsive, focusing on the synthesis and biomedical applications of polymer based nanoparticles. . Delivery of genes into neurons can be achieved by optimization the size of nanoparticles, as well as the conformation of their surface. Further a critical overview of their design principles, drug release performance, and therapeutic advantages over conventional nanoparticles is discussed.

KEYWORDS

Polymer nanoparticle, Liposome, Drug accumulation, Drug delivery system, Drug release, Nanoencapsulation, Particle size, Surface property

INTRODUCTION

Polymeric nanoparticles are defined as particulate dispersions or solid particles with size in the range of 1-100 nm. There has been a considerable research interest in the area of drug delivery using particulate delivery systems as carriers for small and large molecules. Particulate systems like nanoparticles have been used as a physical approach to alter and improve the pharmacokinetic and pharmacodynamic properties of various types of drug molecules. Polymeric nanoparticles have been extensively studied as particulate carriers in the pharmaceutical and medical fields, because they show promise as drug delivery systems as a result of their controlled and sustained release properties, biocompatibility with tissue and cells.[1] Classical therapy proved itself useless many times, due to the random distribution of the drug into human body, high systemic toxicity usually associated with drugs (especially anticancer drugs), high hydrophobicity of some biological active substances and low tissues permeability. To

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overcome all these problems, a number of drug targeting techniques were developed: liposomes, microparticles, nanoparticles, drug-polymer conjugates and polymeric micelles.[2] Some studies showed that it is possible to use nanoparticles for the targeting of highly hydrophobic drugs. The pharmacological studies were confirmed by clinical trials, and some of the formulations are in general use, FDA approved the use of Abraxane™, a suspension of paclitaxel loaded nanoparticles for breast cancer treatment.[3]

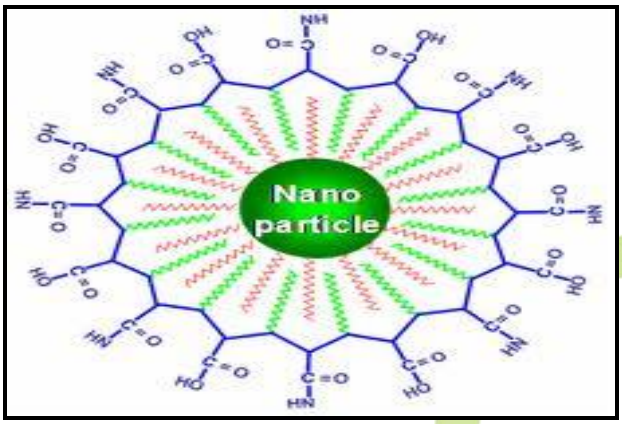

Figure 1: Nanoparticle

In order to be usable in the therapy, nanoparticles should meet several requirements: stability in time, so they can be stored for several months; a long circulating time; assure the biodistribution according to the aim they were developed for; allow the passive or active targetting in the desired area; stimuli responsive (pH, temperature, etc.); usable as a contrast substance for the medical imaging (scintigraphy, ultrasonography, magnetic resonance imaging, computer tomography).[4]

The major goals in designing Polymeric nanoparticles as a delivery system are to control particle size, surface properties and release of pharmacologically active agents in order to achieve the site-specific action of the drug at the therapeutically optimal rate and dose regimen.

Cancer in its myriad forms affects millions of people worldwide and is growing at an alarming rate to become the world's deadliest disease of all times. Till date, the most common methods of cancer treatment are the use of chemotherapy or invasive surgical procedures. Conventional chemotherapy however does not discriminate between the cancer cells and healthy cells thereby causing severe side-effects[6]. Moreover, the systemic delivery of other novel biopharmaceutical anti-cancer agents such as antibodies, hormones, oligo-peptides, nucleic acids, growth factors etc. face significant obstacles from Reticuloendothelial system (RES) and intracellular enzymatic degradation[7,8]. Recently, the use of nanoparticles as delivery vehicles for existing drugs as well as novel cancer therapeutic agents has emerged to be highly effective and possible "game changers" in the field of targeted delivery. These developments are constantly striving to achieve enhanced care and quality of life for cancer patients[9,10]. Several strategies in the design such as nanometer sizes, surface properties, and shape govern the biodistribution, uptake, drug loading capacities, and properties for sustained or controlled release making nanoparticle systems ideal and well suited for cancer therapy[11,12]. Lipid based nano-carriers are amongst the earliest nanoparticles investigated and utilized in variety of therapeutics including cancer. In fact liposomal doxorubicin used in the treatment of Kaposi's sarcoma, breast cancer, and ovarian cancer was the first nano-carrier to receive FDA approval[13]. Further a number of crucial design alterations are in progress to guarantee higher efficacy and effective tumor targeting using receptors such as folate or integrins which are highly expressed on variety of cancer cells[14-18].

Polymer-mediated delivery systems along with lipid nanoparticles have provided the foundations for the field of advanced nanotechnology based drug delivery. Polymeric nanometer sized particles such as micelles, nanospheres, nanocapsules, polymerosomes, polyplexes, and hydrogels etc have been particularly in the limelight as nano-carriers[19]. Polymer carriers offer a large versatility in both structure and physiochemical properties due to a wide variety of available monomers that may be used to form the polymer architectures. Drugs loading is accomplished by infusing the NPs

with drugs in aqueous phase resulting in highly ordered cage like or capsule conformations along with more advanced methodologies include trapping drugs by chemical cross-linking, modifying surface properties of NPs etc[20,21].

A number of polymeric NPs are in the preclinical phase for the delivery of cancer therapeutics owing to the unlimited potential for targeted delivery. Recently, there has been significant interest in employing synthetic polymers like poly(ethyleneglycol) (PEG),[22] polylactide (PLA),[23] and poly(D,L-lactide–co-glycolide) (PLGA)[24]. Dhar et al.[25] have employed a platimum pt(IV) based PLGA-PEG NP to deliver cisplatin in the form of a prodrug showing significantly improved efficacy in vivo. While these polyesters offer excellent biocompatibility and biodegradability, they have limitations with respect to drug release and stability owing to slow degradation of the polymers[26] (Figure 2).

Additionally, certain polymers contain chemical groups that interact with the surrounding environment and change their properties. These polymers are referred to as stimuli responsive or "smart polymers." Some common environmental stimuli such as pH, ionic strength, temperature, chemical agents, and electromagnetic radiation etc result into changes including degradation, phase separation, surface chemistry, shape, permeability, and mechanical properties to release the therapeutics. Such class of stimuli responsive polymers has been of considerable interest for targeted delivery of cancer therapeutics. Temperature responsive polymeric Nps have been developed based on the lower critical solution temperature (LCST) behavior of polymers like poly (N-isopropylacrylamide) (poly(NIPAAm)) and their copolymers[27-29]. Poly(NIPAAm) and its copolymers can be used to form coreshell micellar structures consisting of an inner hydrophobic core surrounded by an outer hydrophilic shell below its LCST. Hydrophobic drugs can then be loaded inside the inner core safely protected from leakage from the exterior hydrophilic shell.

The drugs can then be easily released by localized heating which causes the exterior shell to become increasingly hydrophilic. (Taillefer *et al*)[30] have shown that by using poly(*N*-isopropylacryamide-*co*-methacrylic acid-*co*-octadecyl acrylate) (Poly(NIPAAm-*co* MAA-*co*-ODA)*)* copolymer, aluminum chloride phthalocyanine (AlClPc), a photoactive anticancer payload was delivered to inhibit the growth of EMT-6 mouse mammary cells. In another study, (Cheng *et al*)[31] used biotin-PEG-*b*-P(NIPAAm*co*- HMAAm) diblock copolymer to bind HeLa cells pretreated with transferrin, indicating that drug loaded polymeric micelles can be manipulated to release their cargo by thermally induced structural changes to the micellar core. Temperature responsive polymeric NPs or micelles have been mainly employed as drug delivery vehicles in vitro experiments. The next big step will be to design systems to respond to subtle changes in temperatures targeted at the local tissue sites with greater control over drug release. On the other hand, pH responsive polymers have also emerged as novel stimuli-responsive nanocarriers. For example, (Devalapally *et al*)[32] demonstrated that pH-sensitive poly(ethylene oxide) (PEO)-modified poly(beta-amino ester) (PbAE) nanoparticles lack systemic toxicity and efficiently delivered paclitaxel[32]. While a number of thermal and pH responsive co-polymers with pNIPAAm have been discussed[33], many of them can also be categorized into a novel class of hydrogels for drug delivery[20,34].

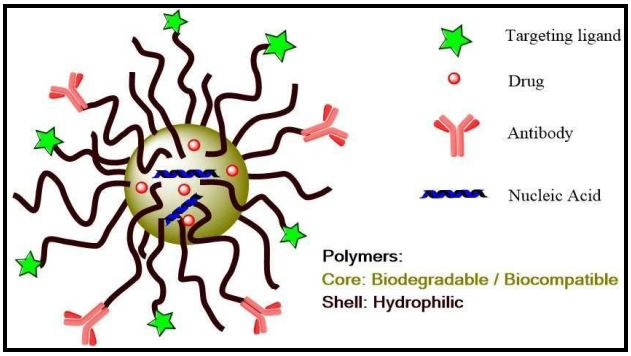

Figure 2: Schematic representation of a polymeric nanoparticle for targeted drug delivery

All nanoparticles in general benefit from enhanced permeation and retention (EPR) effect and result into an increased extravasation into the tumour interstitium, however a thorough careful engineering of polymer nanoparticles including functionalization with targeting ligands is needed to promote receptor mediated uptake into the cancer cells. On the contrary, targeting to tumor vasculature endothelia occurs relatively quickly and does not require extravasation of the nanocarriers[35]. A variety of ligands including folate, transferrin, antibodies or their fragments, and peptides can be conjugated to polymeric nanoparticles to target plethora of receptors commonly over expressed on a number of cancer types[26,36-38]. Targeted polyester based nanocarriers including Poly(lactic acid) and poly(lactic-co-glycolic acid), Poly(ε-caprolactone) functionalized with folate ligands. RGD peptide[39,40] and several other ligands are discussed. Several polysaccharides such as chitosan and cyclodextrins are used to prepare nanocarriers for drug delivery because they offer outstanding physical and biological properties and plenty of reactive groups for functionalizing ligands or reacting drugs. Chitosan nanoparticles has been extensively studied for targeted drug delivery using folate[41], RGD[42] and several other ligands[39]. Additionally, a wide variety of poly amino acids, peptides, and proteins are often coupled with variety of ligands to design targeted biopolymer nanocarriers[39]. In a different approach, epidermal growth factor (EGF) receptor targeted cancer nano carriers have gained considerable attention as these receptors are over expressed on cancer cells[43], (Milane et al).

Preparation of Polymeric Nanoparticle

In the preparation of Polymeric nanoparticles different types of matrix material are used such as polysaccharides, synthetic polymer and proteins. Various factors are involved in selection of matrix material to be used in preparations which are-

(i) Required nanoparticle size.

(ii) Permeability and surface charge of nanoparticle.

(iii) Level of biodegradability and biocompatibility must be optimum.

(iv) Material must not be toxic.

(v) Solubility profile and stability of drug should not be affected.

(vi) It should show desired drug release profile.

(vii) Must not be immnunogenic.

Following are methods which are used in formulation of nanoparticles-

1) From the dispersion of preformed polymer –

a) Solvent evaporation

b) Nanoprecipitation

c) Emulsification/solvent diffusion

d) Salting out

e) Dialysis

f) Supercritical fluid technology (SCF)

2) From polymerization of monomers -

a) Emulsion

b) Mini emulsion

c) Micro emulsion

d) Interfacial polymerization

e) Controlled/Living radical polymerization (C/LRP)

3) Ionic gelation or coacervation of hydrophilic polymers

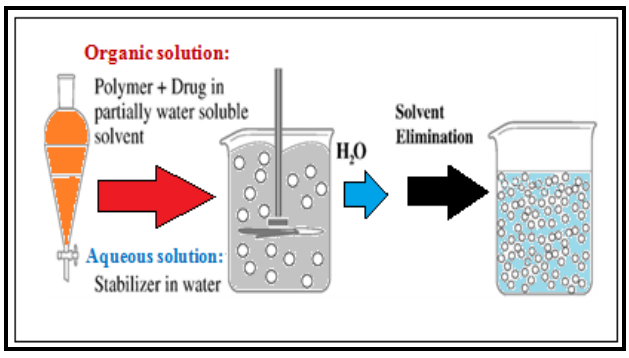

Figure: 3 Schematic representation of a Polymeric nanoparticle with Drug loading

Effect of Characteristics of Polymeric Nanoparticles on Targeted Drug Delivery

Particle Size

Particle size and size distribution are the most important characteristics of nanoparticle systems. They determine the *in vivo* distribution, biological fate, toxicity and the targeting ability of nanoparticle systems. In addition, they can also influence the drug loading, drug release and stability of nanoparticles[44]. Many studies have demonstrated that nanoparticles of sub-micron size have a number of advantages over microparticles as a drug delivery system[45]. Generally nanoparticles have relatively higher intracellular uptake compared to microparticles and available to a wider range of biological targets due to their small size and relative mobility. Drug release is affected by particle size. Smaller particles have larger surface area, therefore, most of the drug associated would be at or near the particle surface, leading to fast drug release. Whereas, larger particles have large cores which allow more drug to be encapsulated and slowly diffuse out[46]. Smaller particles also have greater risk of aggregation of particles during storage and transportation of nanoparticle dispersion. It is always a challenge to formulate nanoparticles with the smallest size possible but maximum stability.

Surface Properties of Polymeric Nanoparticles

When nanoparticles are administered intravenously, they are easily recognized by the body immune systems, and are then cleared by phagocytes from the circulation[47]. Apart from the size of nanoparticles, their surface hydrophobicity determines the amount of adsorbed blood components, mainly proteins (opsonins). This in turn influences the *in vivo* fate of nanoparticles[47,48]. Binding of these opsonins onto the surface of nanoparticles called opsonization acts as a bridge between nanoparticles and phagocytes. The association of a drug to conventional carriers leads to modification of the drug biodistribution profile, as it is mainly delivered to the mononuclear phagocytes system (MPS) such as liver, spleen, lungs and bone marrow. The zeta potential of a nanoparticle is commonly used to characterize the surface charge property of nanoparticles. It reflects the electrical potential of particles and is influenced by the composition of the particle and the medium in which it is dispersed. Nanoparticles with a zeta potential above (+/-) 30mV have been shown to be stable in suspension, as the surface charge prevents aggregation of the particles. The zeta potential can also be used to determine whether a charged active material is encapsulated within the center of the nanocapsule or adsorbed onto the surface.

Drug Loading

Ideally, a successful nanoparticulate system should have a high drug-loading capacity thereby reduce the quantity of matrix materials for administration. Drug loading can be done by two methods:

- Incorporating at the time of nanoparticles production (incorporation method)
- Absorbing the drug after formation of nanoparticles by incubating the carrier with a concentrated drug solution (adsorption/absorption technique).

Drug loading and entrapment efficiency very much depend on the solid-state drug solubility in matrix material or polymer (solid dissolution or dispersion), which is related to the polymer composition, the molecular weight, the drug polymer interaction and the presence of end functional groups (ester or carboxyl)[49-51.]

Drug Release

To develop a successful nanoparticulate system, both drug release and polymer biodegradation are important consideration factors in Target delivery system. In general, drug release rate depends on:

1) Solubility of drug;
2) Desorption of the surface bound/adsorbed drug;
3) Drug diffusion through the nanoparticle matrix;
4) Nanoparticle matrix erosion/degradation;

5) Combination of erosion/diffusion process.

The membrane coating acts as a barrier to release, therefore, the solubility and diffusivity of drug in polymer membrane becomes determining factor in drug release. Furthermore release rate can also be affected by ionic interaction between the drug and addition of auxillary ingredients. When the drug is involved in interaction with auxillary ingredients to form a less water soluble complex, then the drug release can be very slow with almost no burst release effect ; whereas if the addition of auxillary ingredients e.g., addition of ethylene oxide-propylene oxide block copolymer (PEO-PPO) to chitosan, reduces the interaction of the model drug bovine serum albumin (BSA) with the matrix material (chitosan) due to competitive electrostatic interaction of PEO-PPO with chitosan, then an increase in drug release could be observed[52].

Various methods which can be used to study the *in vitro* release of the drug are:

1) Side-by-side diffusion cells with artificial or biological membranes;
2) Dialysis bag diffusion technique;
3) Reverse dialysis bag technique;
4) Agitation followed by ultracentrifugation/centrifugation;
5) Ultra-filtration or centrifugal ultra-filtration techniques.

Usually the release study is carried out by controlled agitation followed by centrifugation. Due to the time-consuming nature and technical difficulties encountered in the separation of nanoparticles from release media, the dialysis technique is generally preferred.

Applications of Polymeric Nanoparticles

Tumour Targeting using Nanoparticulate Delivery Systems

The rationale of using nanoparticles for tumour targeting is based on

1) Nanoparticles will be able to deliver a concentrate dose of drug in the vicinity of the tumor targets via the enhanced permeability and retention effect or active targeting by ligands on the surface of nanoparticles;

2) Nanoparticles will reduce the drug exposure of health tissues by limiting drug distribution to target organ.

Recently (Bibby *et al*)[53] reported the biodistribution and pharmacokinetics (PK) of a cyclic RGD doxorubicin- nanoparticle formulation in tumorbearing mice[53]. Their biodistribution studies revealed decreasing drug concentrations over time in the heart, lung, kidney and plasma and accumulating drug concentrations in the liver, spleen and tumor. The majority injected dose appeared in the liver (56%) and only 1.6% in the tumour at 48 hrs post injection, confirming that nanoparticles have a great tendency to be captured by liver. This indicates the greatest challenge of using nanoparticles for tumour targeting is to avoid particle uptake by mononuclear phagocytic system (MPS) in liver and spleen.

When conventional nanoparticles are used as carriers in chemotherapy, some cytotoxicity against the Kupffer cells can be expected, which would result in deficiency of Kupffer cells and naturally lead to reduced liver uptake and decreased therapeutic effect with intervals of less than 2 weeks administration[54]. Moreover, conventional nanoparticles can also target bone marrow (mononuclear phagocytic system tissue), which is an important but unfavorable site of action for most anticancer drugs because chemotherapy with such carriers may increase myelo suppresive effect. Therefore, the ability of conventional nanoparticles to enhance anticancer drugs efficacy is limited to targeting tumours at the level of mononuclear phagocytic system (MPS)-rich organs. Also, directing anticancer drug-loaded nanoparticles to other tumoural sites is not feasible if a rapid clearance of nanoparticles occurs shortly after intravenous administration.

Long Circulating Nanoparticles

To be successful as a drug delivery system, nanoparticles must be able to target tumours

which are localized outside mononuclear phagocytic system (MPS)-rich organs. In the past decade, a great deal of work has been devoted to developing so-called "stealth" particles or PEGylated nanoparticles, which are invisible to macrophages or phagocytes[55]. A major breakthrough in the field came when the use of hydrophilic polymers (such as polyethylene glycol, poloxamines, poloxamers, and polysaccharides) to efficiently coat conventional nanoparticle surface produced an opposing effect to the uptake by the mononuclear phagocytic system (MPS)[55,56]. These coatings provide a dynamic "cloud" of hydrophilic and neutral chains at the particle surface which repel plasma proteins[57,58]. As a result, those coated nanoparticles become invisible to MPS, therefore, remained in the circulation for a longer period of time. Hydrophilic polymers can be introduced at the surface in two ways, either by adsorption of surfactants or by use of block or branched copolymers for production of nanoparticles[54,55]. Targeting with small ligands appears more likely to succeed since they are easier to handle and manufacture. Furthermore, it could be advantageous when the active targeting ligands are used in combination with the long-circulating nanoparticles to maximize the likelihood of the success in active targeting of nanoparticles.

Reversion of Multidrug Resistance in Tumour Cells

Anticancer drugs, even if they are located in the tumour interstitium, can turn out to be of limited efficacy against numerous solid tumour types, because cancer cells are able to develop mechanisms of resistance[59]. These mechanisms allow tumours to evade chemotherapy. Multidrug resistance (MDR) is one of the most serious problems in chemotherapy. MDR occurs mainly due to the over expression of the plasma membrane pglycoprotein (Pgp), which is capable of extruding various positively charged xenobiotics, including some anticancer drugs, out of cells[59]. In order to restore the tumoral cells' sensitivity to anticancer drugs by circumventing Pgp-mediated MDR, several strategies including the use of colloidal carriers have been applied. The rationale behind the association of drugs with colloidal carriers, such as nanoparticles, against drug resistance derives from the fact that Pgp probably recognizes the drug to be effluxed out of the tumoral cells only when this drug is present in the plasma membrane, and not when it is located in the cytoplasm or lysosomes after endocytosis[60].

Targeting of Nanoparticles to Epithelial Cells in the GI Tract using Ligands

Targeting strategies to improve the interaction of nanoparticles with adsorptive enterocytes and M-cells of Peyer's patches in the GI tract can be classified into those utilizing specific binding to ligands or receptors and those based on nonspecific adsorptive mechanism. The surface of enterocytes and M cells display cell-specific carbohydrates, which may serve as binding sites to colloidal drug carriers containing appropriate ligands. Certain glycoproteins and lectins bind selectively to this type of surface structure by specific receptor-mediated mechanism. Different lectins, such as bean lectin and tomato lectin, have been studied to enhance oral peptide adsorption[61,62]. Vitamin B-12 absorption from the gut under physiological conditions occurs via receptor-mediated endocytosis. The ability to increase oral bioavailability of various peptides (e.g., granulocyte colony stimulating factor, erythropoietin) and particles by covalent coupling to vitamin B-12 has been studied[63,64]. For this intrinsic process, mucoprotein is required, which is prepared by the mucus membrane in the stomach and binds specifically to cobalamin. The mucoprotein completely reaches the ileum where resorption is mediated by specific receptors.

Corticoids Release

Corticoids are anti-inflamatory drugs with high efficiency in the treatment of posterior segment eye diseases such as uveitis. It has also been proved that corticoids can improve the wound healing and they may be effective in the case of fibrosis (proliferative vitreoretinopathy and subretinal neovascularization). (Gomez *et al)*[65] presented the synthesis of dexamethasone

loaded PLGA nanoparticles. Dexamethasone is a poorly soluble crystalline corticoid generally used in the treatment of diabetic macular edema (as an implantable device).

Nanoparticles for Gene Delivery

Polynucleotide vaccines work by delivering genes encoding relevant antigens to host cells where they are expressed, producing the antigenic protein within the vicinity of professional antigen presenting cells to initiate immune response. Such vaccines produce both humoral and cell mediated immunity because intracellular production of protein, as opposed to extracellular deposition, stimulates both arms of the immune system[66]. The key ingredient of polynucleotide vaccines, DNA, can be produced cheaply and has much better storage and handling properties than the ingredients of the majority of protein-based vaccines. Hence, polynucleotide vaccines are set to supersede many conventional vaccines particularly for immunotherapy. However, there are several issues related to the delivery of polynucleotides which limit their application. These issues include efficient delivery of the polynucleotide to the target cell population and its localization to the nucleus of these cells, and ensuring that the integrity of the polynucleotide is maintained during delivery to the target site.

Nanoparticles for Drug Delivery into the Brain

The blood-brain barrier (BBB) is the most important factor limiting the development of new drugs for the central nervous system. The BBB is characterized by relatively impermeable endothelial cells with tight junctions, enzymatic activity and active efflux transport systems. It effectively prevents the passage of water-soluble molecules from the blood circulation into the CNS, and can also reduce the brain concentration of lipid-soluble molecules by the function of enzymes or efflux pumps[67].

Consequently, the BBB only permits selective transport of molecules that are essential for brain function. Strategies for nanoparticle targeting to the brain rely on the presence of and nanoparticle interaction with specific receptor-mediated transport systems in the BBB. For example polysorbate 80/LDL, transferrin receptor binding antibody (such as OX26), lactoferrin, cellpenetrating peptides and melanotransferrin have been shown capable of delivery of a self non transportable drug into the brain via the chimeric construct that can undergo receptor-mediated transcytosis[69-72].

CONCLUSION

Cancer therapy has seen extra ordinary growth in the past two decades due to the advent of variety of strategies to design and functionalize nanocarriers, and a huge selection of therapeutics including drugs, nucleic acids, antibodies etc.

Compared to free drugs, nanocarrier-encapsulated drugs preferentially accumulate in the tumour sites through the EPR effects, thereby improving therapeutic outcomes and reducing side-effects. Targeting of nanocarrier can further improve the efficiency and specificity of drug delivery. A wide variety of targeted nanocarriers have been developed and demonstrated efficacy *in vivo*.

Incorporation of active targeting agents will continue to play a crucial role in the delivery of therapeutic agents. Polymer systems offer immense flexibility in customization and optimization of nanocarriers to efficiently deliver new therapeutics and provide an integral step in aiding their progression to clinical practice. Although the current investigations on targeted, multifunctional and stimuli-responsive polymeric nanoparticles are encouraging, there is a pressing need for careful evaluation in terms of physicochemical properties *in vivo*, pharmacokinetics, bio-distribution, and biodegradability.

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