



Polymeric Nano-Particles for Tumor Targeting – A Review

Ashish Patel, Sakshum Khanna, Gauravi K Xavier, Kushagra Khanna* and Bhawna Goel

Institute of Research and Development, Gujarat Forensic Sciences University, BS Anangpuria Institute of Pharmacy, Faridabad, Haryana, India

*Corresponding author: Kushagra Khanna, Institute of Research and Development, Gujarat Forensic Sciences University, BS Anangpuria Institute of Pharmacy, Faridabad, Haryana, India, Tel: 9428839782; E-mail: sakshum.khanna@gmail.com

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Abstract

Polymeric nanoparticles are nano scale drug carrier. It can be modified by various surface modification reactions and the surface properties can be changed by covalent binding as well as adsorption of various agents which mimics ligand for specific receptors of cell. In addition, these ligands are used for target specific drug delivery and for diagnostic purpose, termed as theragnostic agent. According to polymer properties, we can deliver hydrophobic or hydrophilic drug to a specific target. This review focuses on various techniques of targeting the nanoparticles to a specific site, along with this various preparation techniques, patent invention and their future prospects.

Keywords: Polymeric nanoparticles; Salting out method; Control/Living radical polymerization; Ring opening polymerization; Macro initiator; Radio sensitizer; Spin penetration; Desolvation of macromolecules; Micro tube pumping; Enhanced permeation and retention effect

Introduction

Since the genesis of Nanotechnology and nanoparticles, the field of polymeric nanoparticles (PNP) is broadly expanding and playing a crucial role in a wide spectrum of areas ranging from medicine to biotechnology, pollution control to environmental technology [1]. Nanoparticles (10 to 1000 nm) are formulated or engineered to carry an array of moieties in a controlled manner and to achieve a greater pharmacological response [2,3]. Targeted and tumor-directed therapies are required to improve the outcome and reducing the toxicity [4]. With this, conjugation of drug-loaded nanoparticles along with targeting moieties can be used for receptor-mediated and targeted delivery [5-7].

The use of nanoparticles has a number of advantages viz. targeting, enhancements of therapeutic effect, enhancing permeability, dose reduction and toxic effects as well as availability in parenteral, pre-orals and topical [8,9]. Among the new drug delivery systems, polymeric nanoparticles have been considered as favorable and rising carriers for anticancer agents [10]. Moreover, these polymeric colloidal systems, after i.v. administration, may extravasate solid tumours and infected sites, where the capillary endothelium is defective, thus the tumor site is passively targeting via drug loaded nanoparticles [11].

Polymeric nanoparticles offer significant edge over other nano-carrier, primarily since a tremendous versatility in polymer matrices allows for tailoring the nanoparticle properties. In addition, ease of production, ease of surface modification, encapsulation efficiency, payload protection, slow or fast polymer degradation and stimuli-responsive polymer erosion for temporal control over the drug release, and can easily be scaled-up and manufacturing under Current Good Manufacturing Practices (cGMP) guidelines [12].

The polymer matrix of the nanoparticles must meet several requirements such as biocompatibility, easily biodegradable, better mechanical strength, and easy processing. For controlled release, the best known class of biodegradable materials is the poly (lactide- co-glycolide)s (PLGAs). Following the trend of green polymers, widely accepted and used are biopolymers viz. bovine serum albumin (BSA), human serum albumin (HAS), collagen, gelatin, and hemoglobin have been explored regarding their application to drug delivery systems [13,14].

Advantage of Nano Formulation

In comparison to conventional cancer treatments, the nano scale of these particulate systems also lowers the irritant reactions at the injection site [2].

1. Nanotechnology-based delivery systems can also protect drugs from degradation.
2. Due to decrease in the size the available enhanced product may vary in their physical properties.
3. Reduction in dose frequency.
4. Economic and Patient compliance.
5. Insoluble drugs can also be delivered using Nano-based delivery systems.
6. Nano-based systems can also incorporate previously rejected drugs or drugs with administration issues.
7. Due to specific pathophysiological feature of the diseased tissues, drug targeting is refined and improved.
8. An ideal targeting system should have longer circulating time and optimum concentration at target site.
9. Its pharmacological activity is not affected by longer circulating time.
10. Enhanced permeability and retention effect are characteristic features of tumor, aiding drug delivery.
11. Macrophages (liver and spleen) are passively targeted by drugs.
12. Blood Brain Barrier is the most efficient and challenging natural barrier for CNS targeting drugs which are Lipophilic. For such drugs nanotechnology is the simplest solution as such drugs reach the target site via ultra-filtration process due to its nano-size.
13. Enhance the oral bioavailability of the agents that are not effectively used orally.

Conventional Method of Preparation

Conventionally, two approaches are employed in synthesis of NPs: Pre-formed polymers dispersion method; and Monomer polymerization (Figure 1) [15].

Pre-formed polymer dispersion method

Many approaches have been suggested to prepare biodegradable NPs from polymers (PLA, PLG, PLGA and poly E-caprolactone) by dispersing the preformed polymers [16,17].

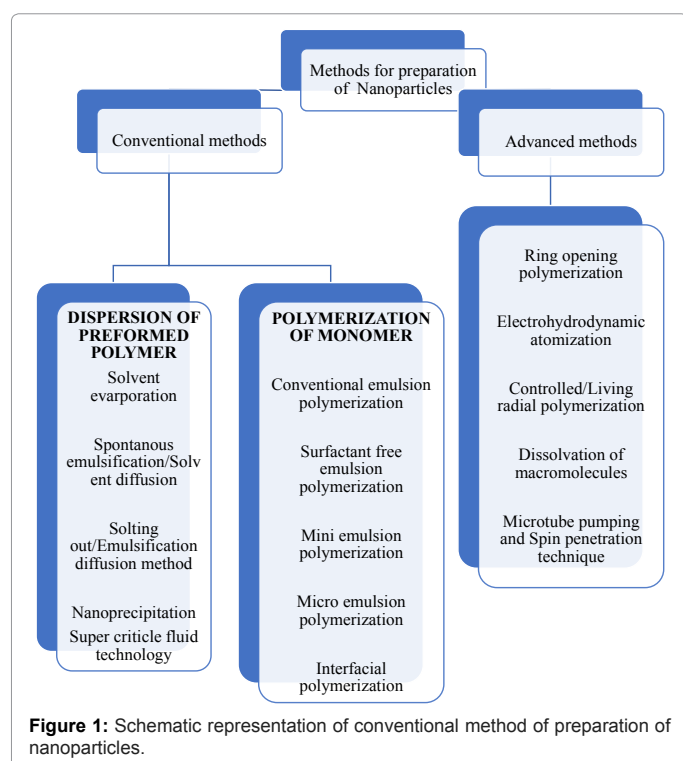


Figure 1: Schematic representation of conventional method of preparation of nanoparticles.

Solvent evaporation method: This method involves, formation of an emulsion, using aqueous and organic phase. The polymer is completely dissolved in the organic solvent (e.g., Dichloromethane, chloroform, ethyl acetate). The drug is dispersed into the above preformed polymer solution. The aqueous solution is added to make an emulsion making an O/W (oil/water) emulsion. To prevent phase separation surfactant/emulsifying agents (gelatin, poly(vinyl alcohol), polysorbate-80,) are added. The end step is to evaporate the organic phase either by temperature and pressure or by continuous stirring [18].

Spontaneous emulsification/solvent diffusion technique: This is an upgraded approach of the conventional solvent techniques (evaporation) [19], in which the oil phase consists of a water-soluble organic solvent (acetone, methanol) and water insoluble solvent (dichloromethane, chloroform) as oil phase. Aqua is used as the aqueous phase. Upon mixing the water soluble organic phase spontaneously diffuse into the water and thus precipitating out the water insoluble organic phase contain the drug as polymeric nano-particles. The remaining aqueous phase is then subjected to evaporation resulting in polymeric NP. The formation of NP's depends upon the Oil-to-polymer ratio and offers advantages over the conventional methods.

Salting out/emulsification–diffusion method: Bindschaedler et al. [20] first disclosed a modified version of emulsion process that results in a salting-out process which avoids surfactants and chlorinated solvents. Polymer and drug are firstly dissolved in a water-miscible solvent such as acetone, it is then emulsified more like Ouzo effect [21], into aqueous gel containing a salting agent (electrolyte: $MgCl_2$, $CaCl_2$; non-electrolyte: Sucrose). Dilute it with sufficient water to facilitate the acetone diffusion into aqueous phase resulting in salting out as nanosphere/particles. Both the solvent and salting agent are removed via cross-flow filtration. The selection of appropriate salting agent is vital as it plays an important role in the encapsulation process of making the nanoparticles [22,23].

Nanoprecipitation: This approach is also known as solvent

displacement method. The preformed polymer dissolved into the organic layer is precipitated out by diffusion of organic solvent into the aqueous medium by either using surfactant [24]. The polymer (PLA), is dissolved in a water-miscible solvent of intermediate polarity, its diffusion into aqueous phase leading to the precipitation of nanoparticles [25].

Production of NPs using supercritical fluid technology:

Conventional methods (solvent evaporation, coacervation and in situ polymerization) involve the use of toxic solvents and/or surfactants. The current green approach is the use of Super-critical fluids. This method utilizes CO_2 in its supercritical state where it provided the advantage of both liquid and gas, and above all is environment safe. Easy regulation of temperature, pressure, higher purity of NP's and minimum-to-no solvent residue are the attractive features of this approach [11].

The NP's are prepared via two methods, RESS (Rapid Expansion Supercritical Solution), RESOLV, SAS (solvent anti solvent).

RESS method is a simple approach which utilizes Supercritical CO_2 as a solvent. The material of interest is completely dissolved into it, and drawn out of a nozzle by varying its temperature/pressure, thus precipitating out the NP's and CO_2 released as a gas. This is a clean technique as no residue of solvent remains. It is highly favourable for bio-erodible drug loaded polymers. The major drawback of this technique is the limited molecular mass (10,000) and solubility in $SC-CO_2$ [26,27].

RAS, a simple, but significant modification to RESS involves spreading of the supercritical solvent into a liquid solvent and also termed as RESOLV [28]. The liquid solvent apparently suppresses the particle growth in the expansion jet, thus making it possible to obtain primarily nano-sized particles.

In SAS method, is widely accepted for the drug-polymer which cannot be dissolved into $SC-CO_2$. The drug-polymer is dissolved in a solvent which favours the $SC-CO_2$. When the $SC-CO_2$ is introduced into the solvent-drug-polymer mixture, at high pressures, enough anti-solvent will enter into the liquid phase so that the solvent power will be lowered and the solute precipitates. After precipitation, when the final operating pressure is reached, the anti-solvent flows through the vessel so as to strip the residual solvent. This method, also called as gas anti-solvent (GAS) technique [29].

Polymerization of monomers

Conventional emulsion polymerization: In this conventional system, the ingredients are comprised of surfactant, water, a monomer of low water solubility, and a water-soluble initiator. Colloidal stabilizers may be electrostatic, electrostatic, steric or exhibiting both stabilizing mechanisms. Initiation appears when a monomer molecule dissolved in the continuous aqueous phase of collides with an initiator molecule that might be a free radical or ions. Alternatively, through high-energy radiation the monomer molecule can be changed into an initiating radical. Formation of solid particles and phase separation can occur before or after the termination of the polymerization reaction [30].

Surfactant-free emulsion polymerization: The varying quantities of surfactants are being utilized in the process of conventional emulsion polymerization systems, but there is need to eliminate those surfactants from the final product. Removal of surfactants increases the cost of production and is a slow process. Moreover, increasing energy and environmental concerns cannot be effectively addressed because of these drawbacks. As a substitute, emulsion polymerization has been performed in the absence of added emulsifier, often referred to as

emulsifier-free, surfactant-free, or soap-less emulsion polymerization [31,32]. This technique has received considerable attention, to be used as a simple, green process for PNP production without the addition of stabilizing surfactant as well as for its subsequent removal.

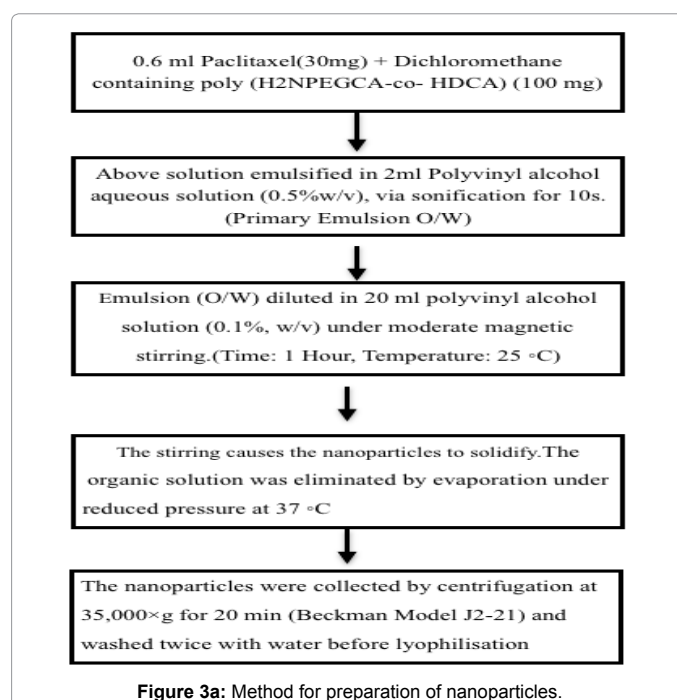
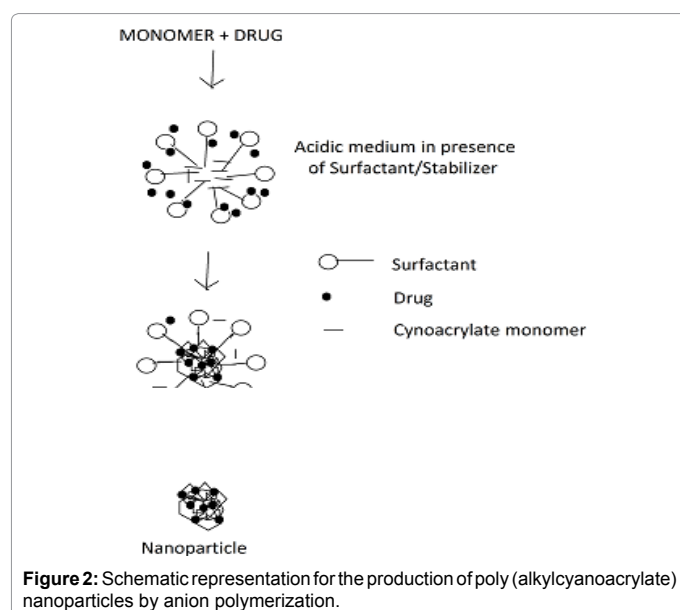
Mini-emulsion polymerization: A distinctive formulation used in mini-emulsion polymerization consists of monomer mixture water, initiator co-stabilizer, and surfactant. A low molecular mass compound acts as the co-stabilizer and also the use of a high-shear device (ultrasound, etc.) is the main difference between mini-emulsion polymerization and emulsion polymerization.

The critically stabilized Mini-emulsions require a high-shear to reach a steady state and have an interfacial tension much greater than zero. With various co-stabilizers and initiator combinations versatile PNPs are well developed in the present era [33].

Micro-emulsion polymerization: The new and effective approach that has attracted significant attention for preparing nano sized polymer particles is a micro-emulsion polymerization. Although micro-emulsion polymerization and emulsion appear similar the reason being both methods can produce colloidal polymer particles with high molar mass but they are entirely different when compared kinetically. Micro-emulsion polymerization exhibits two reaction rate intervals, whereas in emulsion polymerization three are detected. Both the average number of chains per particle and particle size are considerably smaller in micro-emulsion polymerization [34]. In the process of micro-emulsion polymerization a water soluble initiator is added to the aqueous phase of swollen micelles that are thermodynamically stable micro emulsions. The polymerization starts with the spontaneous formation of thermodynamically stable state and relies on high quantities of surfactant systems, which possess an interfacial tension, close to zero at the oil/water interface.

Interfacial polymerization: The Interfacial polymerization is one of the well-established methods used for the preparation of polymeric nano-particles [35]. It involves step i.e., polymerization of two reactive monomers or agents, which are dissolved respectively in two phases (i.e., dispersed-phase and a continuous phase), and the reaction takes place at the interface of the two liquids [36].

Preparation of nanoparticles can also be done by polymerization



of monomers (Figure 2). Poly (alkylcyanoacrylates), PACA, being biodegradable is used to formulate nanoparticles by polymerization method. Here, the cyanoacrylic monomer under vigorous and continuous stirring is added to an aqueous solution of surface-active agents (polymerization medium) at ambient temperature to polymerize the alkyl cyanoacrylate. Drug is then dissolved in the polymerization medium either before the addition of the monomer or at the finish of the polymerization reaction. The NP suspension is then purified by ultracentrifugation or by re-suspending the particles in an isotonic surfactant free medium [37].

Different Methods for Preparation of Nanoparticles

Drug loading into the NPs is achieved by two methods: firstly, by adsorbing the drug after the formation of NPs by incubating them in the drug solution or secondly, by incorporating the drug at the time of NP production. It is thus evident that a large amount of drug can be entrapped by the process of incorporation when compared to the adsorption [38,39].

The kind of surface-active materials and stabilizers has an effect on drug loading [40]. Beside adsorption and incorporation, a novel method of drug loading for the water-soluble drugs was proposed by Yoo et al. [41-43]. In this method, drug was chemically conjugated into NPs, spontaneous emulsion solvent diffusion method was used to prepare conjugates of doxorubicin-PLGA and doxorubicin-loaded PLGA nanoparticles and found to have good encapsulation efficiency of 96.6% as well as 3.5% loading of nano-particles (Figure 3a).

Using the ring opening polymerisation technique, studies show the preparation of H₂N-PEG-PLA, which uses H₂N-PEG as micro initiator [44] (Figure 3b).

Electro hydrodynamic atomization

This new method was first utilised by Xie et al. [45] who developed nanoparticles by electro hydrodynamic atomization (EHDA) of a PLGA solution using acetonitrile. This basic phenomenon has been laid by sir Raileigh who described the possibility to diffuse the fluid in small

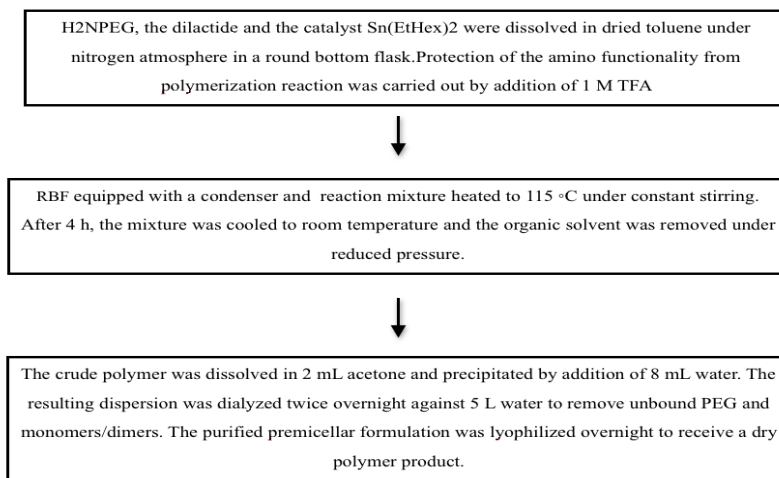


Figure 3b: Method of preparation of H₂N-PEG-PLA.

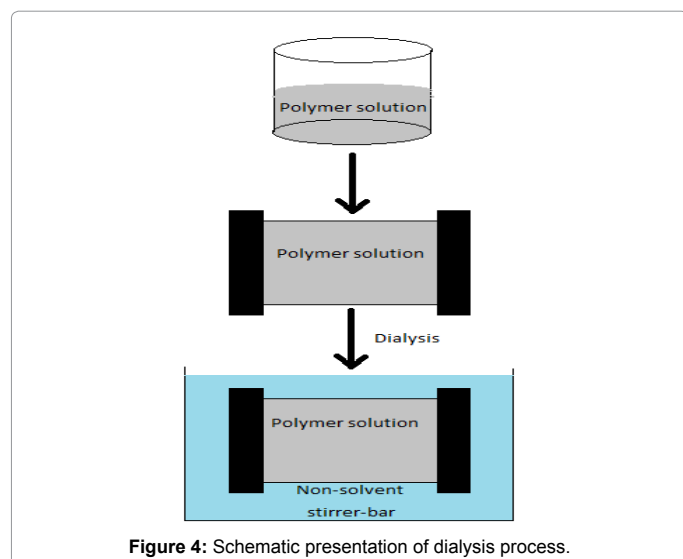


Figure 4: Schematic presentation of dialysis process.

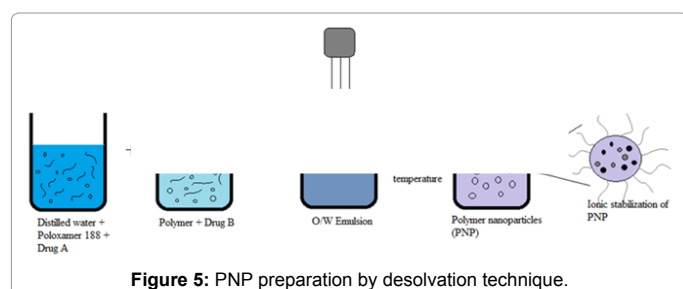


Figure 5: PNP preparation by desolvation technique.

electrically charged droplets under the influence of an electrostatic field. Due to the electrostatic charge on droplets, maximum charge is displayed on the surface of the particles which further produces repulsion and thus, nanoparticle forms.

Controlled/Living Radical Polymerization (C/LRP)

The recent emergence of controlled or 'living' radical polymerization (C/LRP) processes has opened a new area using an old polymerization technique [46-48]. Implementation of C/LRP in the industry is important for developing aqueous dispersed systems that result in the

formation of polymeric nanoparticles with reduced particle size and narrow size distribution.

Among the available controlled/living radical polymerization methods, mainly three approaches are presently successful and extensively studied viz. nitroxide-mediated polymerization (NMP) [49-52], atom transfer radical polymerization (ATRP) [53,54] and reversible addition and fragmentation transfer chain polymerization (RAFT) [55,56].

Dialysis

Dialysis offers an easy and most effective method for the preparation of small, narrow-distributed PNP [57-59]. Polymer is solubilised in an organic solvent and placed inside a dialysis tube with proper molecular weight cut-off. Dialysis was carried out against a non-solvent miscible with the former miscible and the displacement of the solvent inside the membrane is followed by the developmental stage of polymer aggregation due to less solubility and the formation of homogeneous suspension (Figure 4). It is thought that it may be based on a mechanism similar to that of nano-precipitation [60]. A number of polymer and copolymer nanoparticles [61,62] were obtained by this method.

Nanoparticles Produced by Desolvation of Macromolecules

Another technology that is useful for a wide range of polymers is based on addition of a desolvating agent or by desolvation by charge and pH changes, (ethanol or concentrated in-organic salt solutions) (Figure 5).

The main advantage of this process is that it does not require high temperature and, therefore, may be useful when heat sensitive drugs are used [63]. This process offers the advantage of producing nanoparticles directly in aqueous suspension, but, use of potentially toxic compounds such as glutaraldehyde and desolvating agents requires subsequent purification [64]. Nano-particle produced by the desolvation process, unfortunately have comparatively low yield [65]. In case of gelatine, different methods such as the two-step desolvation method [66,67] have been applied to produce nanoparticles.

High Pressure Homogenization

Now a day, production of nano-particles is through widely spread

proven technology known as High-pressure homogenization (HPH). A formulation of paclitaxel is prepared by solvent-free method using serum albumin (3%-4%) known as Nab-paclitaxel which is converted to nanonization by utilising HPH technology, resulting in a colloidal solution [55]. This solvent-free 130 nm particle produced for paclitaxel, has been designed to overcome the problems associated with Kolliphor EL [68-70].

Micro Tube Pumping and Spin Penetration Techniques

This technique used to achieve controlled drug release, as per literature paclitaxel (Ptx)-loaded poly (lactic-co-glycolic acid) (Ptx-PLGA-NPs), (PLGA) nanoparticles were prepared by the emulsion-solvent evaporation method and then transferred to the luminal surface and inside ePTFE vascular grafts through micro tube pumping and spin penetration techniques [71].

Loading of Ptx-PLGA-NPs to an ePTFE Graft

Before loading, silicon tube was connected in the ePTFE vascular graft which has a same in-ternal diameter (6 mm) as that of the external diameter of that silicon tube. The aqueous solution containing Ptx-PLGA-NPs of various concentrations was circulated through the tube and the graft with a micro tube pump at a flow rate of 1.91 mL/min for 30 min. Then, the graft with the Nanoparticles on its luminal surface was fixed in a polypropylene tube vertically connected to a directly driven stirrer. The NPs of the luminal surface of the graft were infiltrated into the inner part of the graft due to centrifugal force in action arise from spinning of the direct driven stirrer (1000 rpm) for 10 min. The above process was repeated three times, and then the NP-loaded grafts were freeze-dried overnight [71].

Targeting to Cancer Cell

The delivery of nanoparticles to specific sites can be through size dependant passive targeting or by active targeting in which, passive targeting depends on both tumor structure and the structure of surrounding inflamed tissues (reference). The nanoparticulate delivery systems may exploit a characteristic of solid tumors by the enhanced permeability and retention (EPR) effect in which tumor tissues demonstrate several distinctive characteristics such as hyper vasculature, defective vascular architecture and a deficient lymphatic tissue/system.

Drainage leads to accumulation of macromolecules and retention in tumor cells for a longer period of time (Figure 6). Active targeting has been performed to achieve a high degree of selectivity to specialized tissues and to enhance the uptake of NP's into target areas

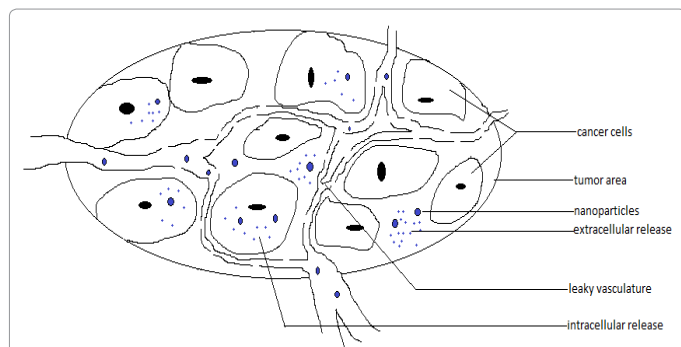


Figure 6: Passive targeting - The combination of leaky casculature and poor lymphatic drainage resultd in the well-known Enhanced Permeability and Retention (EPR) effect [73].

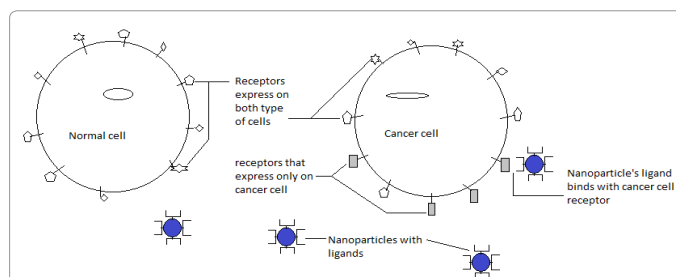


Figure 7: Active targeting involves drug delivery to a specific site based on molecular recognition. One approach is to couple a ligand to nanoparticles which can interact with its receptor at the target cell site [74, 75].

such as cancer cells and angiogenic micro capillaries growing around malignant cells (Figure 7). Nano-particles are modified to target basic characteristics of cancer cells such as accelerated proliferation and particular antigen presentation [72]. Nano-particulate delivery systems utilize specific targeting agents for cancer cells and minimize the uptake of the anticancer agents with the help of normal cells, enhance the entry and release of the agent in tumor cells. These delivery systems include the anticancer agent, a targeting moiety, and a carrier and penetration enhancer. The types of molecules which are capable of specifically recognizing and binding to other biological molecules are antibodies, enzymes, receptor ligands, and receptors. In all cancer therapies, targeting over surface modification provides numerous approaches for increasing treatment specificity and accuracy while reducing toxicity to healthy cells [2].

Passive targeting- The combination of leaky vasculature and poor lymphatic drainage results in the well-known Enhanced Permeability and Retention (EPR) effect (Figure 6) [73].

Active targeting involves drug delivery to a specific site based on molecular recognition. One approach is to couple a ligand to nanoparticles which can interact with its receptor at the target cell site (Figure 7) [74-94].

Ligands that Binds to the Cancer Cell Receptors

Cancer cells have many types of receptors and they are used for targeting purpose. These receptors and their ligands are given below (Table 1). Some agents are used as theragnostic agents, for therapeutic and diagnostic purpose, which are targeted to the specific cell by bonded ligand [95].

Functionalization of Polymer with Ligand for Target Specific Delivery

The modifications in surface of nanoparticulate include coating/ linking with linking with folate, antibodies, adjuvants, proteins, ligands, antigens, enzymes, pH sensitive agents, and a plethora of other substances [1]. PLGA-based nanoparticles grafted with the RGD-peptidomimetic (RGDp), or RGD peptide would target the tumor endothelium and would further enhances the anti-tumor efficacy of PTX. According to *in-vitro* studies, it was found that RGD-grafted nanoparticles were more associated to Human Umbilical Vein Endothelial cells (HUVEC) on binding to $\alpha v \beta 3$ integrin than non-targeted nanoparticles. *In-vivo* studies demonstrated that the targeting of RGD and RGDp-grafted nanoparticles to tumor vessels as well as the effective retardation of TLT tumor growth and extended survival chances of mice treated by PTX-loaded RGD-nanoparticles when compared to non-targeted NP's. Hence, the targeting of anti-cancer drug to tumor endothelium by RGD-labelled NP is a promising approach [96].

Cancer Cell Receptors	Ligands	References
Toll-like receptors	MPLA	[76]
C-type lectins	Mannan	[77]
Siglec	Anti-Siglec-7 polyclonal antibody	[78]
Claudins	CPE30	[79]
$\alpha\beta 1$ integrins	RGD/RGDp LDV/LDVp	[80]
STAT3	JSI-124	[81]
ICAM-1	Clabl	[82]
Folate receptor	Folate	[83]
Specific receptor of lymphatic metastatic tumors	LyP-1	[84]
Prostate specific receptor	PSMA	[85]
$\alpha\beta 3$ integrins	RGD	[86]
Nucleolin	AS1411	[87]
HER-2	rhuMAbHER2	[88]
Transferrin receptor	Lactoferrin	[89]
Opioid receptor	Simil-opioid peptide (g7)	[90]
Opioid receptor	Simil-opioid peptide (g7)	[91]
Specific brain receptor	Pep TGN	[92]
Antibody binding site on cell	Monoclonal antibody	[93]
Proteins, Phospholipids, Sugar on the cell	Aptamer	[94]

Table 1: Ligands that binds to the cancer cell receptors.

It was concluded that vitamin E TPGS (d- α -Tocopheryl polyethylene glycol 1000 succinate) has great advantages for the manufacture of controlled release polymeric nanoparticles of paclitaxel and other anti-cancer drugs. Nanoparticles of with narrow distribution can be obtained with drug encapsulation efficiency as high as 100% and the release kinetics can also be controlled [97].

The targeting characteristics of Polystyrene-latex nanospheres (PSL-NS, mean diameter, 85 nm) coated with (LPS, high affinity to hepatocytes) was evaluated at hepatocytes and PSL-NS surfaces [98]. Hepatocytes were adhered specifically with the lactosyl-polystyrene coated dishes made of the same materials as PSL-NS. Surface modification of biodegradable and long-circulating polymeric nanoparticles has been achieved mainly by two methods: (i) surface coating with hydrophilic polymers/surfactants; and (ii) use of hydrophilic segments to develop biodegradable copolymers.

PEG and PEO-coated NPs

A model for repulsion of proteins from the solid substrate was proposed by Joen et al. [99] which delivers a basis for the prevention of opsonin deposition. The PEG with high surface density and long chain lengths are necessary for low protein adsorption and above all coated PEG increases the systemic circulation of nanoparticles. The nanoparticles shows lower up-take in the liver but shows higher uptake in spleen because of removal of PEG coating so it is useful in spleen targeting [100].

An attempt was made to study the effect of surface density of PEO on the compliment consumption by using diblock polymer of PLA and polyethylene oxide (PLA-PEO) Vittaz et al. [101]. It was observed that as the PEO density on the surface of the Nanoparticles increases with the decrease in compliment consumption due to steric repulsion of the surface to proteins.

Poloxamine and Poloxamer Coated NPs

In a study conducted by Illum and Davis [102], long-circulating NP's of polystyrene and poly (methyl methacrylate) were developed

with a coating of poloxamer and poloxamine. It was observed that hepatic uptake decreased about 20% with poloxamer-188 and 40% with poloxamer-338, whereas a decrease about 60% was observed for poloxamine-908 coated na-noparticles. As a result poloxamine was considered more effective coating material to avoid the liver capture of rabbits as compare to poloxamer [103].

Cyclodextrin/Carbohydrate Coated NPs

Mononuclear phagocyte system (MPS) is the natural defence mechanism by which the body prevents any unwanted entry of pathogens. Many times nanoparticles are subjected to MPS leading to its phagocytosis or elimination. Incorporation of carbohydrate coating over the nanoparticles of interest was found to by-pass the MPS uptake, as reported by Cho et al. [104]. For DNA, targeted delivery NPs of PLA and poly (L-lysine)-grafted-polysaccharide were developed [105]. They were found to be resistant to self-aggregation or clumping and adsorption (non-specific) of serum proteins.

The nanoparticles whose surface was coated with Cyclodextrin was found to increase loading efficiency of water soluble drugs and also the bioavailability of drugs that are poorly water soluble and are considered for targeted delivery. Another approach to achieve higher loading capacity of drug and to increase the stability of parent Cyclodextrin the Poly (isobutylcy-anoacrylate), PIBCA nanoparticles, coated with hydroxypropyl or natural Cyclodextrin are used.

Polysorbate-Coated NPs to Penetrate the Blood-Brain Barrier

Blood Brain Barrier is the most efficient barrier system in the entire human body, making it difficult for the transportation of drugs (hydrophilic and similar) across it. Thus it becomes mandatory to enhance the drug transport. There have been suggested mechanisms to enhance the drug transport across BBB (Figure 8) via coated NPs such as:

- (i) Binding to inner endothelial lining of brain capillary, thus, particles deliver drugs by providing a difference in concentration gradient, thus improving the passive diffusion
- (ii) By phagocytosis [106].

Studies show a higher permeation across the biological matrices and membranes, when nano-particles are coated with surfactants, e.g., polysorbate-80 coated NP's [107]. It was show-cased (Troster et al.) [108], a 9-fold increase in accumulation of radioactivity in the cerebral area post I.V. administration using polysorbate-80 coated radioactive (14C)-PMMA nanoparticles. A 60-fold increase in brain concentration was reported (Gulyaev et al. [109], when doxorubicin was bound to polysorbate-80 coated PBCA nanoparticles which were systemically administered.

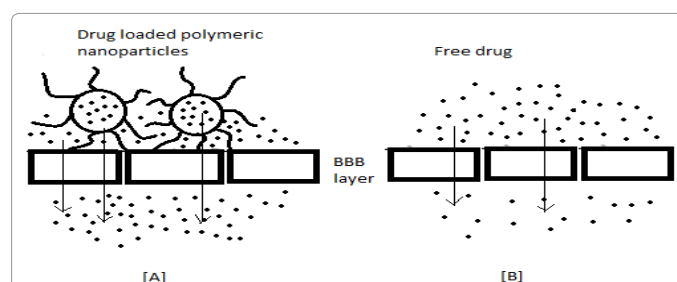


Figure 8: Drug loaded polymeric nanoparticle (A) deliver higher amount of drug across BBB as compare to free drug (B).

Drug	Summary of Invention	References
Docetaxel	Docetaxel nanoparticle coated with PLGA block copolymer conjugated with low mol. Wt. PSMA ligand.	[111]
Curcumin	Polymeric nanoparticle coated N-isopropylacryl amide (NEPAAM), acrylic acid (AA), and at least one vinyl monomer selected from the group consisting of vinyl acetate, 4-vinyl benzoic acid etc..	[112]
Dexamethasone	Dexamethasone coated with chitosan chloride and/or chitosan glutamate by ultrasound sonication.	[113]
Beclomethasone	Beclomethasone coated with a diblock poly (lactic) acid-poly (ethylene) glycol copolymer; 1,2 distearoyl-sn-glycero-3-phosphoethanolamine poly(ethylene)glycol copolymer by ring opening polymerization techniques (ROMP).	[114]
Curcin	Curcin planetary ball milled (PBM) nanoparticles coated alginate, cellulose, collagen, starch and PEG conjugated with folate.	[115]
Mitoxantrone	Mitoxantrone coated with polyethylenes, polycarbonates, polyanhydrides etc. Conjugated with PSMA.	[116]
Carbazitaxel	Carbazitaxel coated with diblock poly (lactic) acid-poly(ethylene)glycol conjugated with a low-molecular weight PSMA ligand.	[117]
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Curcin	Curcin planetary ball milled (PBM) nanoparticles coated alginate, cellulose, collagen, starch and PEG conjugated with folate.	[115]
Mitoxantrone	Mitoxantrone coated with polyethylenes, polycarbonates, polyanhydrides etc. Conjugated with PSMA.	[116]
Carbazitaxel	Carbazitaxel coated with diblock poly (lactic) acid-poly(ethylene)glycol conjugated with a low-molecular weight PSMA ligand.	[117]
Calcium channel blocker	Drug Np comprise hydroxy-terminated or epoxide-terminated and/or activated multiblock copolymer modifying the surface by lyophilization technique to produce a physically adsorbed coating and epoxy-derivatization to functionalize the surface.	[118]
Paclitaxel	Paclitaxel coated with PLGA conjugated with galactosamine targeting ASGP receptor by emulsion/solvent evaporation method	[119]
Gefitinib	Gefitinib nanoparticle drug delivery systems including a modified PLGA-b-PEG block copolymer.	[120]
Paclitaxel	Paclitaxel coated with Poly(2-(dimethylamino)ethyl methacrylate-co-methacrylic acid(PDM) targeting to cancer cell.	[121]
5-fluorouracil	5-fluorouracil coated by bovine serum albumin conjugated with folate by coacervation method.	[122]
Paclitaxel	Paclitaxel coated with Human serum albumin by emulsion solvent evaporation method	[123]
Paclitaxel	Gelatin PLGA nanoparticles containing paclitaxel coated with bioadhesive molecules	[124]
Ganciclovir	Hollow protein nanoparticles containing ganciclovir encapsulating thymidine kinase (HSV1tk) modified to display a hepatitis B virus surface-antigen for hepatocyte recognition	[125]
Ganciclovir	Nanoparticle of Ganciclovir containing thymidine kinase modified with epidermal growth factor receptor	[126]
Cetuximab	Composition and method for targeting cancer cell by administering Cetuximab in combination with tetrac or triac	[127]
Resveratrol	Resveratrol coated with polymer functionalized with RGD peptide, which is recognized by $\alpha v \beta 3$ receptor	[128]

Table 2: Patent invention and future prospect.

Formulation of Actively Targeting Nanoparticles (ATN) prepared (solvent evaporation) by conjugating transferrin to PEG-coated biodegradable polycyanoacrylate NP, for the enhanced delivery of Paclitaxel. Resulting, Avg. Encapsulation Efficiency=93.4 ± 3.6%; Particles Size=101.4 ± 7.2 nm; Zeta potential=(-13.6 ± 1.1 mV) [110-128].

Patent Invention and Future Prospect

Nanotechnology holds an advantage in formulating nature derived products (Table 2). Nanoparticles-mediated natural products delivery diminishes the toxicity to healthy cells [129]. Studies claim a considerable improvement in treatment using nanotechnology in comparison to the conventional methods for cancer such as chemopreventive/therapeutic approaches. Nano-technology also portrays a promising future in the areas of diagnosis, imaging, and therapeutics. A large of research in nanotechnology is dedicated to enhance the science of nanoparticles as a drug delivery system. Considerable amount of Construct, based on principles of nanotechnology have presently on-

going clinical development and also pre-clinical development, with a few having achieved FDA approval.

Achieving a forefront in the application of nanotechnology, with a focus on herbal/naturally derived products will aid us in building drug systems with viable and tangible results against numerous diseases [130,131]. There has been voiced a concern regarding the universal safety as well as environmental effects and common health effects on those included into manufacturing sciences, these points in questions will be addressed in due course of time [132].

Conclusion

The Polymeric nanoparticles are manufactured and modified by surface modification reaction for target specific drug delivery and it can also be used for delivering hydrophobic drug. The surface modification of polymeric nanoparticle is used to improve the systemic circulation, drug loading and enhancement in controlled drug delivery. Certainly, modification in surface is useful in achieving these goals.

From the chemistry viewpoint, it is important to synthesize polymers and copolymers to meet the hydrophilic and hydrophobic properties. Production of Nanoparticles using the eco- friendly processes like supercritical fluids is a promising area of research to develop products which are free from the unwanted toxic residual solvents. Various patents are on targeting of polymeric nanoparticles. Different types of methods are used for preparation of nanoparticles and improve drug loading in dosage form (PNP). Nanotechnology is promising in Novel Drug Delivery System and it is emerging field in Pharmaceutical field.

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