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REVIEW ARTICLE

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Polymeric Nanoparticles - the new face in Drug Delivery and Cancer Therapy

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ABSTRACT

Nanotechnology has been widely focused throughout the world for their efficacy, specificity, tolerability and therapeutic index of the drugs. Nanoparticles (NPs) mediated targeting plays a significant role in inhibiting inflammation, angiogenesis and tumor progression. Especially polymeric NPs have greater deal that provides numerous properties such as simple to synthesize, inexpensive, biocompatible, biodegradable, non-toxic, non-immunogenic and water soluble for an effective drug delivery and drug targeting. This review discusses recent advancement in the development of drug delivery and drug targeting using polymeric NPs for an efficient anti-cancer therapeutics. As these polymer based NPs has high mobility in the smallest capillaries, allowing for efficient uptake and selective drug accumulation at the target sites for a competent cancer therapy.

***Keywords*:** *Nanoparticles, polymer, drug delivery, cancer therapy, polylactides, polyglycolides.*

1. INTRODUCTION

Nanoparticles (NPs) generally <100 nm can be used in targeted drug delivery at the site of disease to improve the uptake of poorly soluble drugs, targeting of drugs to a specific site and drug bioavailability [1,2]. Drugs can either be integrated in the matrix of the particle or attached to the particle surface. A drug targeting system should be able to control the fate of a drug entering the biological environment [3-7]. These method will be effective in treating a variety of illness such as, diabetes, osteoporosis, Alzheimer's, Parkinson's, neurological disorders, multiple sclerosis, HIV-1 associated neuro-cognitive disorders, cardio vascular disorders, tuberculosis and cancers [8-13]. Nanoparticles mediated targeting plays a significant role in inhibiting inflammation, angiogenesis and tumor progression [14]. In recent years, nanotechnology has been widely focused on by numbers of researchers throughout the world for their efficacy, specificity, tolerability and therapeutic index of the drugs [15]. There are numerous NPs based drug delivery system available includes: liposomes, micelles, dendrimers, solid lipid NPs, metallic NPs, semiconductor NPs and polymeric NPs, among these polymeric NPs have shown considerable attention in the last two decades as a multifunctional nanotechnology based delivery system for poorly water-soluble drugs [16]. Polymer–drug conjugation promotes tumor targeting through the enhanced permeability and retention effect and at the cellular level following endocytic capture, allows lysosomotropic drug delivery [17].

2. SIGNIFICANCE OF POLYMERIC NANOPARTICLES

Polymeric NPs are particles which are prepared from polymers. A polymer is a class of natural or synthetic substances composed of macromolecules that are multiples of monomers. Because of their broad range of properties, both synthetic and natural polymers play an essential and ubiquitous role in everyday life. Polymers range from familiar synthetic plastics such as polystyrene to natural biopolymers such as DNA and proteins that are fundamental to biological structure and function. Polymers, both natural and synthetic, are created via polymerization of many monomers. Polymeric NPs has greater attention in the last two decades as a multifunctional nanotechnology-based drug delivery system.

The drug is dissolved, entrapped, encapsulated or attached to polymeric NPs and depending upon the method of preparation, NPs, nanospheres or nanocapsules can be obtained. Polymeric nanocapsules are vesicular systems in which the drug is confined to a cavity surrounded by a polymer membrane, while nanospheres are matrix systems in which the drug is physically and uniformly dispersed. Polymeric carriers avoid the interaction of the drug with macromolecules such as proteins, which could sequester the active ingredient preventing its arrival at the action place. A polymer used in controlled drug delivery formulations, must be chemically inert, non-toxic and free of leachable impurities. It must also have an appropriate physical structure, with minimal undesired aging, and be readily processable.

2.1. PROPERTIES OF POLYMERIC NANOPARTICLES

If a polymeric carrier is to be used, the next step is to design a type of polymeric structure that should be biodegradable, because the chemical bonds that make up its chemical structure break; disassemblable, because the various pieces forming the polymer disassemble but the chemical bonds do not break; and undisassemblable, because the chemical bonds do not disassemble or break, that is, the polymer remains unchanged [18]. Polymer based NPs has greater advantages than other nanomaterials for its increased in stability of any volatile agents, easily fabricated in to larger quantities, oral and intravenous methods of administration with significant efficiency and effectiveness, drug delivery with higher concentration with greater significant target and the choice of polymer and ability to alter drug release from polymeric NPs have made a better ideal candidate for delivery of targeted drugs, delivery of vaccines and for cancer therapy. Polymers used in the preparation of polymeric NPs are natural hydrophilic includes (proteins and polysaccharides). Synthetic hydrophobic includes (pre-polymerized and polymerized in process).

In spite of development of various synthetic and semi synthetic polymers, natural polymers still enjoy their popularity in drug delivery; some of them include Gums (Eg. Acacia, Guar etc.), Lectin, Viciline, Dextran, Chitosan, Gelatin, Sodium alginate and Albumin. However, in recent decades additional polymers are considered primarily for medical applications and have entered the competition with of controlled release of bioactive agents. Many of these materials are designed to degrade within the body such as Polyglycolides (PGA), Polylactides (PLA), Poly (D, L-lactide-co-glycolides – PLGA), Polyanhydrides, Polyorthoesters, Polycyanoacrylates and Polycaprolactone. Among them PLGA, PLA and PGA are most extensively investigated due to its good biocompatibility and biodegradability [19].

2.2. POLYMER NANOPARTICLES IMPACT ON DRUG DELIVERY APPROACH

The benefit of these biodegradable polymers retains their properties for a limited period of time *in vivo* and then gradually degrades into materials that can become soluble or metabolized and excreted from the body. However, biodegradable materials produce degradation by-products that must be tolerated with little or no adverse effects within the biological environment. The polymer chosen to formulate the NPs will strongly affect the structure, properties and application of the particles. For each application and drug of choice it must evaluate the properties of the system (drug and particle) and determine whether or not it is the optimal formulation for a given drug delivery application (i.e.) the presence of a carboxylic end group on (PLGA) play a significant role in the preservation of the protein drugs activity throughout the drug release duration. Therefore choice of such polymers can have multiple impacts on each polymer drug systems. Abraxane is the first polymeric NPs based product from American Pharmaceutical Partners, Inc., and American Bioscience Inc., (ABI). It was approved in year 2005 and is consisting of albumin-bound paclitaxel NPs. Success of Abraxane show that nanotechnology can bring many exciting products which can overcome many hurdle of formulation [20,21].

The modified delivery of the active ingredient site other than that of administration is classified on the basis release such as extended release and sustained

release formulations. Extended release is defined as the release of the active ingredient in these formulations is initially produced in a sufficient amount to produce a therapeutic effect and then to continue with a release over a longer period of time, which is not necessarily constant but extends the therapeutic action (i.e.) a polymeric matrix that contains the active ingredient, the delivery of which is controlled by diffusion through the polymeric system network. These formulations are presented in the form of hydrogels and NPs and micro particles. The other type of extended-release formulation comprises API (active pharmaceutical ingredients) capsules with polymer coatings, forming a reserve deposit. The permeability or the degradation of the polymer coating regulates the release of the drug [18, 22].

Sustained release formulations are designed to release a drug at a predetermined rate in order to maintain a constant drug concentration for a specific period of time with minimum adverse effects. This can be achieved through a variety of formulations, including drug-polymer conjugates (an example being hydrogels- water-absorbing polymers). As the tablet passes through the body, the osmotic pressure of water entering the tablet pushes the active drug through the opening in the tablet. Once the active ingredient in the Oros tablet has been released, the remnant is excreted [18, 22].

2.3. POLYMER BASED NANOPARTICLES IN CANCER THERAPEUTICS

Nanomedicine, especially drug formulation by polymeric NPs, has shown a great deal of promise to provide solutions to such problems in cancer treatment [19]. Among the most commonly used polymers are PLA and PLGA, which have been approved by the food and drug administration (FDA) for the development of drug delivery systems and other biomedical applications. Degradation by non-enzymatic hydrolysis of PLA and PLGA leads to an accumulation of acidic monomers, which causes a decrease in pH. When the encapsulated therapeutic agent is a protein it may denaturalize. Conversely, these two polyesters are the most widely used because of their non-toxic degradation products and adjustable degradation rate [18].

The most important challenge in the successful formulation of polymeric drug delivery systems involves preparing carrier systems that could be capable of encapsulating the preferred drug within its structure and then deliver the drug to the target (cancerous tissues). Particle size is an important parameter as it directly affects the physical stability, cellular uptake, biodistribution and drug release from the NPs. In a recent drug delivery study the author has reported that curcumin (natural plant based product) encapsulated in PLGA nanosphere solid-in-oil-in-water (s/o/w) solvent evaporation technique exhibited high yield and drug entrapment efficiency. The *in vitro* curcumin release studies from the nanospheres revealed that curcumin was released in a sustained manner over a prolonged period of time. Intracellular uptake and cell viability assays also demonstrated efficient uptake and action of the curcumin nanospheres in prostate cancer cell lines. Therefore author reveals that PLGA nanospheres are capable of delivering curcumin over a prolonged period achieving a sustained delivery of curcumin, for potential candidate for cancer therapy [23].

Polylactides and Poly (D,L-lactide-co-glycolides based NPs are rapidly cleared in the liver and captured by the reticulo endothelial system (RES) when they are administrated into the blood circulation [24], therefore in a separate study [25], introduce D-α-tocopheryl polyethylene glycol 1000 succinate (TPGS) into the hydrophobic PLA backbone. TPGS which are water-soluble derivative of the natural form of D-α-tocopherol, is formed by esterification of vitamin E succinate with poly-ethylene glycol (PEG) 1000 [25]. The author also reported that TPGS improves the aqueous solubility of drugs including antibiotics, cyclosporines, steroids and inhibits p-glycoprotein that increases the cytotoxicity and oral bioavailability of anti-tumor agents [25, 26]. Tang, [26] reported a novel delivery systems of Cholic acid (CA) (polyhydroxy initiator) a star-shaped block copolymers (for faster hydrolytic degradation rates) based on PLA and TPGS known as (CA-PLA-TPGS NPs) with unique architectures revealed sustained and controlled delivery of paclitaxel for breast cancer treatment and achieved higher drug loading content and entrapment efficiency, resulting in faster drug release as well as higher cellular uptake and cytotoxicity. The *in vivo* cell studies indicated that the PTX-loaded star-shaped CA-PLA-TPGS NPs reported to have significantly superior anti-tumor activity [26].

Tao et al., 2013 has demonstrated a novel copolymer docetaxel-loaded M-PLGA-TPGS NPs, (modified nanoprecipitation method), were observed to be near-spherical shape with narrow size distribution. The author reported that the uptake level of M-PLGA-TPGS NPs observed higher than that of PLGA NPs and PLGA-TPGS NPs in MCF-7 breast cancer cells. Also a significantly higher level of cytotoxicity found with docetaxel-loaded M-PLGA-

TPGS NPs. The *in vivo* experiment animal model data revealed docetaxel-loaded M-PLGA-TPGS NPs has the highest anti-tumor efficacy in treating breast cancer [27]. Mattu et al., 2013 prepared NPs by a modified single emulsion solvent evaporation method with five different polymers: three commercial polyesters (poly (ε-caprolactone) (PCL), poly (d,l-lactide) (PLA) and (PLGA)) and two novel biodegradable polyesterurethanes (PURs) based on Poly(ε-caprolactone) blocks, synthesised with different chain extenders (1,4-cyclohexane dimethanol (CDM) and N-Boc-serinol). The extent of cellular internalisation was analysed on two different cell lines: MCF-7 and SK-BR-3 breast cancer cells that have normal and a high expression of the HER-2 receptor, respectively [28]. Paclitaxel, a anti-neoplastic drug, was encapsulated inside all NPs, and release profiles and cytotoxicity on SK-BR-3 cells was assessed that reveals, PUR NPs was superior to commercial polyester-based NPs in terms of higher cellular internalisation and cytotoxic activity on the above breast cancer cell lines [28].

Paul et al., 2013 has demonstrated the encapsulation of chelidonine in biodegradable (PLGA) polymers and evaluated nano-chelidonine's (NCs) anti-cancer efficacy vis-a-vis free chelidonine (FC) against HepG2 cells and demonstrated its bioavailability in experimental mice model. Nano-chelidonine's exhibited rapid cellular uptake and stronger apoptotic effect than FC, blocking HepG2 cells at G2/M phase. p53, cyclin-D1, Bax, Bcl-2, cytochrome c, Apaf-1, caspase-9 and caspase-3 expressions also corroborated well to recommend greater anti-cancer potentials of NC. The author further reported that NC to have greater bioavailability with better tissue distribution with toxicity. Therefore the authors reported that NCs could be a better anti-cancer agent [29]. Martin [30], Another study demonstrated PLGA NPs surface-modified with an amidine-based polymer poly (guanidinium oxanorbornene) (PGON) which increase trans-urothelial migration and tumor cell uptake. The author further reveals that PGON-modified NPs increased the cytotoxicity of belinostat, a promising therapeutic agent for cancer. The treatment with belinostat-encapsulated PGON-modified NPs led to prolonged (histone deacetylase inhibitors) HDAC inhibition compared to unencapsulated drug and flank tumor regression in a mouse xenograft bladder cancer model. The polymers used are designed with the capacity to form polymeric supramolecular structures (matrices and capsules), which are suitable for retaining a therapeutic agent and allow controlled release [35]. Wang et al., 2013 shown PLGA NPs modified with chitosan reported an initial burst release followed by a moderate and sustained release. PLGA NPs modified by chitosan reveal versatility of surface and a possible improvement in the efficacy of current PLGA-based drug delivery system [31].

Etoposide (hydrophobic anti-cancer agent inhibiting topoisomerase-II, commonly used in pediatric brain chemotherapy) formulated as a parenteral injectable solution (Teva) was loaded into all-biocompatible (PLGA) or PLGA/P188-blended NPs using a fully biocompatible nanoprecipitation technique which helps in efficient parenteral delivery of etoposide, and as a potential therapeutic candidate [32]. Das et al., 2012 has demonstrated the efficacy of the extract of *Phytolacca decandra* and its PLGA nano-encapsulated form in experimental mice, intoxicated with benzo[a]pyrene (BaP) with sodium-arsenite and on A549 lung cancer cells *in vitro*. The author reported that nano-encapsulation of *Phytolacca decandra* increased the drug bioavailability and thereby has a better chemo-preventive action against lung cancer *in vivo* and on A549 cells *in vitro* than that of *Phytolacca decandra* extract alone [33]. Gonzalo et al., 2013 demonstrated a novel nanocapsules, prepared using a modified solvent displacement technique where the polyamino acid (PGA) was electrostatically deposited on to the lipid core. The author reveals that the *in vivo* studies performed in experimental mice model indicated that encapsulation provides the drug with a prolonged blood circulation and significantly reduced the toxicity. Therefore, this study provides a valid claim that PGA could be used as potential nanocapsules based drug delivery for any anti-cancer therapy [34, 30].

Zheng et al., 2013 reported that NPs could efficiently deliver plasmids into HeLa cells and TRAIL/endostatin-loaded NPs could act as a potential as an ideal candidate for *in vivo* cancer gene delivery. The author demonstrated using biodegradable copolymer, TPGS-*b*-(PCL-*ran*-PGA), which was synthesized and characterized. The NPs was fabricated by an emulsion/solvent evaporation method and modified with polyethyleneimine (PEI) carrying TRAIL and/or endostatin genes. Severe combined immunodeficient mice carrying HeLa tumor xenografts was treated in groups of six including phosphate-buffered saline control, blank TPGS-*b*-(PCL-*ran*-PGA) NPs, blank TPGS-*b*-(PCL-*ran*-PGA)/PEI NPs, and three types of gene NPs. The activity was assessed using average increase in survival time, body weight, and solid tumor volume. The author further reveals that the cytotoxicity of the HeLa cells was significantly increased by

TRAIL/endostatin-loaded NPs when compared with control groups. Thus the use of TPGS in combination with TRAIL and endostatin had synergistic anti-tumor effects. Finally, there is another promising formulation for drug deliveries are dendrimers. Dendrimers is a novel polymer with well defined str-ucture, high molecular uniformity and low polydispersity property that makes them more attractive in development of nanomedicine. Dendrimers based delivery system transports drug across cellular barrier efficiently. Mesoporous silica particle (MSP), layered double hydroxide (LDHS) are used for efficient drug delivery [36]. Recently report shown that dendrimer-doxorubicin increases lymphatic doxorubicin concentrations when compared to the liposome formulation. The dendrimer formulation increased the recovery of doxorubicin in the lymph up to 30 hr post dose compared with the solution and liposomal formulations respectively [37]. These data suggest that dendrimer based drug delivery systems are also have the potential to enhance effective drug exposure to lymph-based drug targets to inhibit lymphatic metastasis.

3. CONCLUSION

Among different delivery systems, polymeric based nano-carriers have numerous properties such as simple to synthesize, inexpensive, biocompatible, biodegradable, non-immunogenic, non-toxic and water soluble. This review focused on a variety of polymer based NPs used in nanoscale cancer therapy. These polymers based NPs has high mobility in the smallest capillaries, allowing for efficient uptake and selective drug accumulation at the target sites for an efficient cancer therapy. The use of polymers as NPs formulation provide greater multifunctional properties in the field of (nanotechnology) NPs based drug delivery vehicles and an efficient targeting for its significant and effective anti-cancer therapeutics.

Conflict of Interest

The authors declare that they have no conflicts of interest

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