REVIEW ARTICLE

Polymeric Nanoparticle-Mediated Targeted Drug Delivery System: A Promising Approach for Breast Cancer

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ABSTRACT

After lung cancer, breast cancer (BC) is the second most frequent malignancy in women globally. Surgery followed by chemotherapy is the conventional treatment plan for BC. However, both are unsuccessful in treating BC because of the harmful effects that these treatments have on healthy tissues and organs. Many polymeric nanoparticles (PNPs) have been discovered and created recently to selectively aim cancer cells without harming normal cells. As an outcome, drug delivery systems (DDS) mediated by NPs have developed as a possible method to treat BC. PNPs have several special qualities that make them ideal for cancer treatment due to their tunable surface functions and choosiness to target tumor cells and minimize side effects

Keywords: Breast cancer, Polymeric nanoparticles, Drug delivery systems, Side effects, Tumor.

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Graphical Abstract

INTRODUCTION

A class of diseases known as cancer is caused by unchecked cell proliferation, and these abnormal cells can invade and spread to other parts of the body. Carcinoma, which encompasses almost all malignancies of the breast, prostate, lung, pancreas, and colon, is one of them. It denotes cancer that arises from epithelial cells.[1] Since ancient times, breast cancer (BC) has been known. The idea that BC was a systemic illness was initially advanced by Hippocrates, known as "the Father of Western Medicine." The "Halsted mastectomy" was the gold standard for more than 50 years, leaving many women with severe disabilities.

Additionally, accounting for nearly 30% of all malignancies, BC is the most commonly prevalent form in females.[2] The American Cancer Society projects that there may be 40,920 fatalities from the 2,66,120 new cases of invasive BC that were found in 2018. By contrast, in males, BC accounts for only 1% of all malignant breast neoplasms. The average age at which males are diagnosed with BC is 67 years old, which is older than that of women. It is believed to be treatable if discovered early, despite being the most common type of tumor in women.[3] But if metastasis happens, cancer can move through the blood and lymph systems to far away organs, rapidly increasing the challenge of treatment and the death rates (Figure 1). The usual treatment for breast cancer is surgery, chemotherapy, and radiation therapy, just like it is for other types of cancer. These therapies' main objective is to get free of tumors while extending patients' lives. Advanced and metastatic cancers, however, provide a challenge to these conventional techniques in terms of lump reappearance and drug resistance. For example, when a cancer returns and spreads to distant organs like the bone, lung, or liver, surgery is ineffective.

Chemotherapy aims to prevent the division and proliferation of cancer cells. Despite being efficient cancer treatment techniques that increase survival rates, radiation and chemotherapy may have detrimental short and long-term consequences on patients' healthy organs.[4] In addition to heart failure, trastuzumab, a monoclonal antibody used as a chemotherapeutic treatment for breast cancer, is hazardous when administered for extended periods. Multidrug resistance is another challenging issue caused by many proteins overexpressing cancer cells. In these cases, chemotherapy frequently has a significantly reduced effect. Radiation is a

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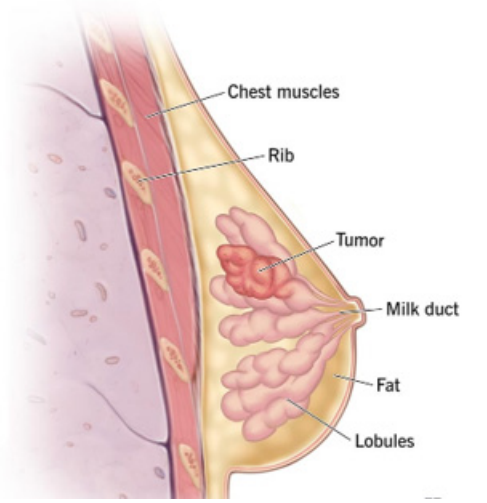

Figure 1: Schematic representation of Breast cancer tumor develops when breast cells mutate and grow

type of limited treatment that first targets the area that contains cancer. Negative effects, however, could occur due to damage to the surrounding healthy tissues.

It has long been noted that the clinical use of many potent therapeutic drugs in the dealing of cancer and other disorders has been constrained for the following reasons:[5,6]

- Low systemic bioavailability due to insufficient water solubility.
- Instability *in-vivo*: Drugs tend to be metabolized and removed by the entire living organism, changing the drug's concentration *in-vivo* and decreasing its efficacy.
- Hazardous side effects: Nephrotoxicity, neurovirulence, and gastrointestinal responses are all always hazardous side effects of the drugs that also affect normal cells.
- Drug resistance: It is simple to develop multidrug resistance and lessen the impact of additional therapy.

Effective substitutes for conventional cancer treatment approaches need to be carefully considered in light of these side effects. In contrast, the usage of NPs as an effective delivery approach for the treatment of cancer has just fascinated certain interests.[7,8] To eliminate the drawbacks of conventional techniques, ongoing research is active to optimize this technology.[9]

Chemotherapy and Side Effects

Dox, a chemotherapeutical of the anthracycline class, is extensively utilized in the clinical management of numerous human malignancies. It is used either alone or in blended with other drugs to treat BC. A great deal of research has been done to realize the negative effects of Dox *in-vivo* and in the clinical setting.[10] It is well recognized for having a significant likelihood of cardiac or gastrointestinal damage. Thus, customized administration may be essential in Dox treatments.

Another significant and well-liked chemotherapeutic drug used to treat BC is paclitaxel (PTX). PTX stimulates tubulin dimerization and inhibits microtubule depolymerization, in contrast to other anti-microtubulin drugs, to provide an anticancer effect.[11,12] Neutropenia and peripheral neuropathy

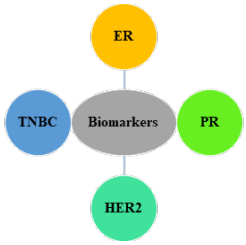

Figure 2: Schematic representation of Biomarkers for evaluating treatment response in Breast cancer

are two well-known adverse effects of PTX. As a result, two important areas of research focus now include PTX dosage optimization and PTX estimation in combination treatment regimens. Additional chemotherapy regimens that are commonly used include docetaxel, cisplatin, trastuzumab, and tamoxifen. The most common side symptoms that patients describe are tiredness, weight loss, marginal neuropathy, and nausea. There have been reports of several serious side effects, including cardiac complications, osteoporosis, lymphedema, and concerns about cognitive abilities.[13]

Biomarkers

A biomarker is an indicator that may be measured and utilized to know biological processes or diseases even when the patient does not have it. Biomarkers are increasingly being used in medicine to diagnose and treat illnesses (Figure 2). Targeted nano drug delivery, which is the primary method of treating BC,[14] involves using nanocarriers to target molecular recognition markers. Utilizing biomarkers in drug delivery makes it easier to aim cancerous cells precisely and less damaging to healthy cells. Because several oncogenes are overexpressed in resistant breast cancers, the beginning and development of various disorders have been linked to biomarkers.

While HER2 overexpression is found in only about 25% of breast tumors, ER overexpression is found in most breast cancers.[15] Triple-negative breast cancers (TNBCs) are the 15% of breast tumors that do not express ER, PR, or HER2. These tumors are thought to be the hardest to cure.

ER

Both inside the cell and on the BC cell membrane are ERs. As mentioned earlier, ER+ type BC breast tumors account for the majority of cases and can impact women before or after menopause. Tamoxifen is the widely recognized antagonist for ER+ breast tumors.[16] El-Sayed *et al*. have also effectively administered tamoxifen-conjugated nanoparticles to emergency rooms. Tamoxifen's efficiency was increased up to 2.7 times over the free drug when cancer cells absorbed the system through the receptor.

PR

PR, also known as PR-A and PR-B, is a type of steroid hormone receptor. PR is also essential for the differentiation of lobuloalveoli. Different forms of endocrine therapy are used clinically to identify individuals with invasive BC. Adjuvant and neoadjuvant therapy phases are among those for which it functions as a predictor.[17]

HER2

The transmembrane glycogen protein known by the name HER2 is divided into three components. It possesses an N-terminal extracellular domain (ECD) and an internal tyrosine kinase domain. The proteins that make up the HER family include HER1, HER2, HER3, and HER4.[18] Subdomains I through IV comprise the ECD, which makes up the majority of HER2. The cysteine-rich subdomains II and IV, respectively, are accountable for homodimerization and heterodimerization. Pertuzumab and trastuzumab, two monoclonal antibodies, are recognized as dimerization inhibitors. By attaching to the dimerization arm of HER2, these obstruct the signal and slow down cell proliferation by preventing dimerization with other members of the same family.

TNBC

TNBC is more lethal because it develops aggressively and fast. Triple-negative basal-type tumors do not make up all of TNBC; only 85% of them are basal-type malignancies. But there are a few protein changes that are unusual in TNBC that can be seen in basal-type tumours. Several receptors, including transferrin, folic acid, arginyl glycyl aspartic acid (RGD), and the epidermal growth factor receptors (EGFR), are expressed in many solid basal-type cancers, including BC.[19] Furthermore, it has been shown that treating TNBC with multiple therapeutic drugs at the same time is more effective.

Polymeric Nanoparticles for Targeted Drug Delivery

They consist of colloidal particles with sizes ranging from several 100 nm. Copolymers are frequently linked to distinct polymer matrices to form these nanoparticles. PNPs offer more wide-ranging characteristics for efficient delivery and drug targeting.[20] They can adopt either nanocapsules or nanospheres as their structural form, depending on how they were formed. In the first instance, the drug is contained in a core and covered in a polymer layer, while it is also possible for the drug to be the core itself. However, nanospheres are loaded with the drug and take the shape of a cross-linked polymer (Figure 3). In either scenario, the medicinal material may potentially infiltrate onto the nanoparticle's surface.

Another significant benefit of PNPs is that the properties of a specific polymeric nanoparticle can be altered by appropriately altering the polymer, allowing for the control of drug release from the nanoparticle at a definite site in the body as well as the ability to make the drug carried water-soluble. On the other hand, a short half-life can be made up for by encasing the drug inside the nanoparticle. Polymeric nanoparticle anticancer therapy is being employed more frequently in studies because it is possible to focus on the therapeutic effect, specifically on cancer cells. Undoubtedly, the small size is most important in cancer therapy, since there is restricted access to the active ingredient.

Biological Ligands for Nanoparticle Drug Delivery Systems

Passive targeting

Through the actions of EPR, nanoparticles (NP) can promote the accumulation of cancer cells. EPR makes a significant contribution to drug accumulation in angiogenic tissues like cancers. Slow lymphatic drainage helps NPs penetrate further into the disease site's vascular structures. The physicochemical characteristics of NPs affect EPR and are easily changed by altering the constituent molecules or the manufacturing procedure.[21]

Nanocarriers can enter cancer cells by endocytosis and deliver more drugs to the cells without having a specific receptor target. Nanomedicine must have a hydrophilic surface and a diameter of <100 nm to prevent increasing drug targeting and enhancing drug circulation in the body. The quantity and dynamics of nanomaterial deposition at the cancer cells are affected by their size.

Active targeting

To aid in the effective targeting of NPs, numerous physiologically significant ligands were discovered and examined. Additionally, these biological ligands fix specific receptors on the target cell membrane. The uptake and therapeutic efficacy of medicines containing NP will be improved through ligand-receptor interactions.[22] Active targeting, which relies on affinity-based identification, retention, and enhanced absorption of the target cells, is employed for tumor precision and delivery efficiency (Figure 4). Target cells will assemble ligand-decorated pharmacologically active molecules (such as antibodies or monoclonal medicines) on the nanocarrier.

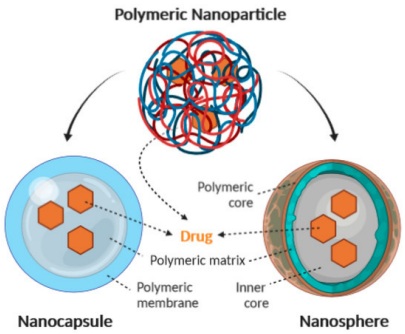

Figure 3: Schematic representation of distinct morphology of a nanosphere and a nanocapsule

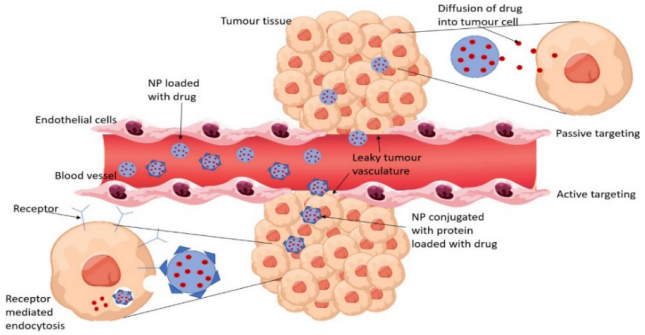

Figure 4: A Schematic illustration of active targeting and passive targeting of Nanoparticles (NP) in anti-tumor therapy

Different kinds of ligands have been employed. They might bind to polymers or be adsorbed to NP. Chemical affinity for active targeting is built on a range of unique molecular interactions, including receptor-ligand-based and charge-based interactions.[23]

A perfect active target moiety should have the following qualities:

- Tumour cells contain more target moieties than normal tissues do.
- Rather than internal targets, it should be assessed at sites that nanocarriers can easily access, such as surface receptors.
- The concentration needs to be high enough to enable accurate targeting.
- Targeting can streamline processes that make drug delivery easier.

Classification

Non-biodegradable polymers

Polymers that are not biodegradable, such as poly (methyl methacrylate), polyacrylamide, polystyrene, and polyacrylates, are utilized to form polymeric nanoparticles (NPs). These nanosystems showed quick and effective clearance, but there was also evidence of long-term toxicity and inflammatory responses.[24]

Several factors can impact biodegradable polymeric nanoparticles, such as their size, structure, and molecular weight, as well as environmental factors like pH and temperature; non-biodegradable polymers usually take longer to break down than their useful application times.

Biodegradable polymers

Synthetic polymers such as poly(D, L-lactide) (PLA), poly(D, L-glycolide) (PLG), copolymer poly(lactide-co-glycolide) (PLGA), polyalkylcyanoacrylates (PACA), and polycaprolactone (PCL) are examples of biodegradable polymers. Biodegradable polymeric particles are generally less harmful to the body and more biocompatible.[25] They are classically broken down into monomers and oligomers that are subsequently metabolized and removed from the body by standard processes.

Synthetic biopolymers

There has been a lot of interest in synthetic biopolymers due to their stability, flexibility, low immunogenicity, and biodegradability. Because they are resistant to hydrolysis and can withstand high temperatures, they can be heat-sterilized without deteriorating.

The production of poly(hydroxy acids), poly (hydroxyalkanoates) (PHAs), poly(lactones), and PACA are the most often utilized classes of synthetic biopolymers.[26]

Polyglycolic acid

The first polymer of this class studied for use in biomedicine was Polyglycolic acid (PLG). Opening the glycolide ring or polycondensing glycolic acid yields it, though, due to its stiffness and quick degradation, it is not a good option for nanocarriers of cancer therapies.[27]

Polylactic acid

Polylactic acid (PLA) is produced by polymerization or polycondensation of lactic acid (LA). It is available in 2 forms, i.e., l and d forms. The usage of PLA does not cause significant immunological reactions meanwhile, the byproducts of PLA biodegradation are quickly eliminated from the body.[28]

Polylactic acid -co-glycolic acid

The most popular copolymer among polyesters is Polylactic acid -co-glycolic acid (PLGA), which is composed of the monomers of glycolic and lactic acids. In aqueous conditions, PLGA polymers entirely biodegrade, and their properties can be reformed by changing their biochemical makeup (lactide/glycolide proportion) and chain length.[29] When the polymer's molecular weight is lowered, the rates of drug release and degradation both increase.

Poly (Ɛ-caprolactone)

It is the polymer most researched for the creation of anticancer drugs among polylactone-based polymers. By polymerizing -caprolactone in a ring-opening manner, it is a semicrystalline substance. The slower rate of Poly (Ɛ-caprolactone) (PCLs) degradation also extends the release of pharmaceuticals that have been encapsulated.

Poly (alkyl cyanoacrylates)

Another type of biodegradable polymers beneficial for making nanocarriers is Poly (alkyl cyanoacrylates) (PACA).[30] The length of the alkyl chain affects the rate of degradation; the slower the rate, the longer the alkyl chain.

Natural biopolymers

Proteins and polysaccharides derived from plants or animals and microbial sources are examples of natural biopolymers. Due to their distinctive qualities, which include biodegradability, biocompatibility, and low toxicity, they are frequently used in drug delivery research.[31] They can, however, be immunogenic and regularly essential to undergo chemical variation before being employed to make nanoparticles.

Animal-Based Biopolymers

Albumin

The blood protein albumin (MW 65–70 kDa) is produced naturally. Nanosystems for anticancer therapy are created using both human and bovine serum albumin. They produce nanoparticles with comparable features and share similar physicochemical properties.[32]

Due to its extended biological half-life, enhances the pharmacokinetics of the drugs and enables the EPR effect to be utilized for higher deposition in cancer tissues, it is employed as a nanocarrier for antitumor chemicals. Albumin nanoparticles are a component in one of the most significant IV paclitaxel formulations used in clinical practice (Abraxane®;).

Gelatin is a heterogeneous blend of polypeptides created when animal collagen is partially hydrolyzed. Two varieties (A or B) of gelatin are produced as a result of this technique. It has

been demonstrated that type B gelatin produces nanoparticles with superior qualities than type A gelatin. The enzymatic breakdown of gelatin into its amino acids depends on several factors, including pH, temperature, and concentration.[33]

Gelatin can be easily changed to carry targeted moieties and is typically inexpensive and widely available.

Hyaluronic acid

For biological and pharmacological purposes, Hyaluronic acid (HA) and its byproducts have been used, particularly for the long-acting, target-specific anticancer drug administration.[34] A mucopolysaccharide called HA is d-glucuronic acid and N-acetylglucosamine, which are connected by alternating 1,4 and 1,3 glycosidic bonds. All living things have it in their intracellular and extracellular matrix.

The development of malignant tumors and the expression of the HA receptor were discovered to be closely related. Lymphatic vascular endothelial hyaluronic acid receptor 1 (LYVE1), hyaluronan-mediated motility receptor RHAMM, and CD44 are among the HA receptors that are triggered in tumor cells to encourage cell intrusion and malignancy. By attaching to these receptors, HA facilitates the absorption of nanoparticles. Covalently conjugating HA to the exteriors of the nanoparticles is another method for enhancing drug delivery and the duration of nanoparticle circulation.

Plant-Based Biopolymers

Animal-derived polymers tend to be more immunogenic than plant-derived polymers, which are prevalent.

Cellulose

It is a linear homopolymer of d-glucopyranose that is 1,4-glycoside-connected. Because it doesn't elicit an immunological response and because opsonization, a crucial stage in the phagocytic clearance of nanoparticles, is suppressed by its very hydrophilic structure, it is appropriate for the formation of nanoparticles.[35] As a result, it extends the time hydrophobic drugs spend in the bloodstream and permits aggregation in the target tissue.

Starch

Another readily available polysaccharide derived from plants is starch. Starch is a form of stored energy that all plants produce; however, it is prevalent in tuberous plants like potatoes and cereals like corn, beans, wheat, and rice. It is converted into glucose units by amylases and glucosidases.[36] This edible polysaccharide's benefits in the field of controlled release include increased drug solubility and stability, harmfulness and fewer side effects, and superior biocompatibility.

Soy protein

It is a very abundant and inexpensive substance. The soy protein's amino acid profile promotes the significant entrapment efficiency of hydrophobic drugs.[37] This can be done by taking advantage of the protein's aqueous solubility properties for various administration methods.

Zein is a low molecular weight protein (20 kDa) found in the endosperm of maize cells. Due to its insoluble nature in water, it is regarded as a viable biomaterial for the formation of nanocarriers containing hydrophobic chemicals.[38]

Biopolymers From Marine Organisms

Chitosan

It is a commonly used cationic polysaccharide permitted by the FDA. It also forms stable complexes with negative substances and is the only naturally occurring positive polysaccharide, an excellent choice for controlled release and drug encapsulation.[39]

Alginate

An anionic linear polymer called alginate is generated from sea brown algae. It is made up of 1,4-glycosidic linkages that connect the residues of -d-mannuronic acid and -l guluronic acid. These connections are susceptible to both alkaline -elimination and acid hydrolysis.[40] Because of its low cost and versatility in interacting with bioactives, it was utilized in the construction of several nanosystems.

Carrageenan

Despite its potential, there isn't any trustworthy study on using carrageenan to yield nanoparticles for anticancer drugs. However, it has been discovered that carrageenan prolongs drug release in mucosal and epithelial tissues.[41]

Approaches of PNP's

Nanoparticles can deliver an extensive range of therapeutic classes, counting anticancer, antifungal, anti-inflammatory, and anti-leishmanial drugs.[42] In general, encapsulation favors a drug's delayed and/or controlled release, and interest in using nanoparticles to transport encapsulated substances to particular organs or cells is developing. Drugs in PNPs have been successfully encapsulated using a variety of techniques.

Emulsification and solvent evaporation method

Its basic principle involves dissolving the polymer in an organic solvent, mixing the organic phase with stabilizers and surfactants in the aqueous phase, emulsifying the mixture, and finally letting the slowly boiling organic solvent evaporate. Organic solvents like chloroform, dichloromethane, and ethyl acetate are frequently employed.[43] Applying heat and vacuum to an organic solvent causes it to evaporate. During the mass manufacture of heat-sensitive PNs, spray-drying is the preferred approach for removing organic solvents.

Nanoprecipitation method

In the nanoprecipitation process, an aqueous phase is gradually mixed with a water-miscible organic phase, either with or without the addition of a stabilizer or surfactant. When a nonaqueous solvent (like acetone) is removed from the solution, the polymer is then left behind at the interface. This simple approach has traditionally been used primarily for the encapsulation of hydrophobic medicinal compounds.[44]

Supercritical anti-solvent method

The supercritical anti-solvent approach is a further technique for making PNs in low-stress environments.[45] In particular, a pressured container holding an anti-solvent liquid like CO_2 is sprayed with a polymeric solution in the form of small

droplets. The emergence of nanoparticles is favored by the quick diffusion of CO_2 into the solution.

Salting-out method

It is based on adding highly concentrated salts (such as $MgCl_2$, $CaCl_2$, and magnesium acetate) or saccharides to a polymeric solution that results in the presence of a coacervate; they can also be attained by adjusting temperature and pH.

CONCLUSION

Millions of women worldwide are affected by BC, which lowers their quality of life. Understanding cancer biochemistry and implementing fresh approaches to BC treatment is necessary for the development of a drug-resistance mechanism. With the development of several combinatorial medicines for BC treatment in recent decades, the fatality rate from BC has decreased. Recent nano-delivery technologies that use particular pairings of nanocarriers and target molecules that are comparable to chemotherapy combination tactics aid in the management of BC. These therapeutic approaches show significant potential and anticipate encouraging outcomes for the treatment of BC patients. Future theranostics based on NDDS will be created to address the various issues with traditional chemotherapy.

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