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Review Paper

PLGA- Based Nanoparticles for Targeted Drug Delivery in Breast Cancer: A Review

Aarchi*, Yogesh Gautam, Dr. Tenzin Wangpo

Dreamz College of Pharmacy, Khilra, Sundernagar, Mandi, Himachal Pradesh,175036.

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ABSTRACT

Breast cancer (BC) remains a significant global health concern, with traditional chemotherapy facing growing resistance. Epigallocatechin-3-gallate (EGCG), the main polyphenol found in green tea, demonstrates strong anticancer effects through multiple pathways; however, its effectiveness is limited by instability and low bioavailability. This study explores the creation and development of biodegradable poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) as a delivery system. Employing surface functionalization techniques (folate/PEGylation) and co-loading methods, these systems enable targeted delivery, improve chemosensitivity in drug-resistant cells, and offer additional renoprotective advantages

INTRODUCTION

Breast cancer is the most commonly diagnosed malignancy among women and a leading cause of cancer-related mortality. Its global burden has risen steadily with urbanization, delayed childbearing, obesity, and lifestyle changes. Breast cancer originates from breast tissue, most commonly from the inner lining of the milk ducts or the lobules that supply the ducts with milk. In 2004, breast cancer caused approximately 519,000 deaths worldwide.

Cancer cells are very similar to the cells of the organism from which they originated and have similar (but not identical) DNA and RNA. This is the reason why they are not often detected by the immune system, particularly if it is weakened. Cancer develops if the immune system does not function properly and/or the number of cells produced is too great for the immune system to eliminate [1].

Death occurrence rates are highest in the very young (less than 35 years) and very old (greater than 75 years). It appears that the very young have more aggressive disease and that the very old may not be treated aggressively or may have comorbid diseases that increase breast cancer fatality [2].

***Corresponding Author:** Aarchi
Address: *Research scholar, Dreamz College of Pharmacy, Khilra, Sundernagar, Mandi, Himachal Pradesh,175036..*
Email ✉: aarchithakur7@gmail.com

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Epigallocatechin gallate (EGCG) is a polyphenolic compound. EGCG is isolated from various plants. Several studies have shown that EGCG has anti-inflammatory, antioxidative, and anti-fibrotic properties, implying that it may be a preventative tool in different metabolic illnesses and their consequences. EGCG enhances organ protection against injury [3]. EGCG, the principal catechin of green tea leaves of Camellia sinensis, exhibits pleiotropic anticancer activity. EGCG affects cancer cells through multiple mechanisms, including altering the cell cycle, inducing apoptosis, inhibiting invasion and metastasis, and modulating the Tumor Microenvironment (TME). These complex interactions demonstrate the potential of EGCG as a multifaceted anticancer agent [4]. The advent of nanotechnology presents novel opportunities to enhance the clinical applications of EGCG. Encapsulating EGCG in nanocarriers has significantly improved its solubility, stability, and bioavailability, facilitating targeted tumor delivery [5].

Poly (lactic-co-glycolic acid) (PLGA) is an FDA-approved, biodegradable polymer that hydrolyzes to polylactic acid and polyglycolic acids. Poly (lactic-co-glycolic acid) (PLGA) nanoparticles (NPs) have been extensively employed in drug delivery owing to their favorable biocompatibility and biodegradability profiles [6]. This is a way to protect EGCG and help it enter the body slowly over time. PLGA acts as a shell that keeps EGCG safe and helps it work better to fight breast cancer. Natural compounds are beneficial in the fight against cancer, both in preventing and treating cancer. Green tea is an example of a natural compound that is beneficial.

1. Selection of Polymer

PLGA: Matrix Polymer

Poly (lactic-co-glycolic acid) (e.g., 50:50 and 65:35 lactide: glycolide) offers biodegradable, biocompatible, and regulatory-validated performance. By selecting the molecular weight and copolymer ratio, the release profile can be tuned from days to weeks. End-group chemistry (acid- vs. ester-terminated) affects the surface charge and interactions. Residual monomers hydrolyze to metabolites that enter the Krebs cycle, supporting safety. PLGA is a synthetic aliphatic polyester that has gained extensive acceptance in pharmaceutical nanotechnology owing to its predictable biodegradation, excellent biocompatibility, and adaptable physicochemical properties. Hence, Poly (lactic-co-glycolic acid) nanoparticles are capable of encapsulating a wide spectrum of therapeutic agents, including hydrophobic chemotherapeutics and hydrophilic drugs, proteins, peptides, nucleic acids and plant chemotherapy, and they also help in chemoprevention[7].

2. Properties of PLGA

Surface engineering: PEGylation and active targeting

PEGylation (PLGA-PEG) reduces opsonization and prolongs circulation. For active targeting, ligands that recognize receptors overexpressed in breast cancer will be explored: folate (folate receptor), hyaluronic acid (CD44), RGD peptides (integrins), transferrin (TfR), or anti-HER2 fragments for HER2-positive lines. The final choice will be aligned with the receptor status of the selected cell lines and validated using competitive binding assays.

3. Formulations of EGCG loaded PLGA-NPs

PLGA Nanoparticles: Proposed carrier

PLGA is a biodegradable polymer approved by the Food and Drug Administration (FDA). It is most widely used in drug delivery because it safely degrades into lactic acid and glycolic metabolites. Nanosized PLGA carriers offer:

1. Nanosized PLGA carries receptor-mediated uptake in targeted design
2. Nanosized PLGA protects EGCG (epigallocatechin gallate) from oxidative degradation.

The selection of polymer manufacturer is critical in determining the performance of drug delivery systems because PLA, PGA, and PLGA obtained from different suppliers may have different properties if the process or catalysts used in their production are different. Consequently, drug delivery companies are tied to one supplier as a source of polymers, and any change in this source may necessitate expensive bridging studies. The following are the leading suppliers of GMP-grade PLA, PGA, and PLGA: Purac, Birmingham Polymers, Boehringer Ingelheim, Alkermes, Sigma Chemical Company, and Polyscience. Other suppliers, including Mitsui Chemicals, cater to local niche markets. Birmingham Polymers offers a range of PLGA copolymers priced at approximately $38–47 per gram. PLA and PLGA are nontraditional excipients in the pharmaceutical industry. While the current demand for these polymers is limited, there is significant growth potential, primarily driven by the development and advances in PLGA drug delivery systems[8].

4. Design and Engineering of the Nano-Platform

Formulation Strategies

Efficient encapsulation of EGCG into the hydrophobic PLGA matrix was achieved through:

1. Double Emulsion (W/O/W): This method helps create a watery core for EGCG. As a result, we obtained an encapsulation efficiency of up to 85 percent.
2. Nanoprecipitation: This technique was used for synthesis. This results in round particles.
3. PEGylation: Addition of polyethylene glycol (PEG) creates a layer. This layer prevented macrophages from taking up EGCG-PLGA. This helps EGCG-PLGA to remain in the system for a longer duration.

5. Targeting and Surface Modification

To change from passive to targeted, nanoparticles are given special helpers called ligands.

1. Folate Decoration: MDA-MB-231 breast cancer cells have many Folate Receptors. When folate was added to the PLGA-EGCG nanoparticles, they worked better at entering the cells and reducing tumors than those without these helpers.
2. Active Ligand Density: It important to determine the amount of these helpers on the nanoparticles so they can bind well to breast cancer cells.

6. Preparation of Nano-particles

The nanoparticles were prepared using a nanoprecipitation method and were composed of a blend of two polymers: poly(epsilon)-caprolactone (PCL) and PLGA-PEG-A, PLGA-PEG-DCL, or PLGA-PEG-AG. Briefly, PCL and PLGA-PEG-ligand conjugated polymer, with a mass ratio of 1.5:1, and EGCG (4%, w/w), were dissolved in acetonitrile and added dropwise under gentle stirring to an aqueous solution of Pluronic F-127 (0.1% w/w), giving a final polymer concentration of 7.0 mg/mL. The resulting suspension was stirred at room temperature to evaporate the organic solvent, followed by centrifugation and washing to remove the non-encapsulated EGCG. EGCG-free NPs (indicated as A-NPs, DCL-NPs, and AG-NPs, based on the polymer used for their preparation, that is PLGA-PEG-A, PLGA-PEG-DCL, and PLGA-PEG-AG, respectively) were produced in a similar manner and used for comparison. Fluorescent FITC-loaded NPs (FITC-NPs) were prepared as mentioned above by adding fluorescein isothiocyanate (FITC) instead of EGCG to different polymer solutions[9].

7. **Preparation of EGCG-Loaded PLGA nanoparticles**

PLGA nanoparticles were prepared using the oil-in-water emulsion solvent evaporation technique. Briefly, for the preparation of EGCG-encapsulated PLGA-NPs, the ratio between the volume of EGCG to the volume of PLGA was 1:20. EGCG (10 mg) was dissolved in deionized water (1 mL) and emulsified with a solution of PLGA (10 mg) dissolved in dichloromethane (1 mL) to form an O/W emulsion. The emulsification was performed using a microtip probe sonicator (Sonics & Materials Inc, Newtown, CT, USA) with a sonicator operating at 200 W over an ice bath. The O/W emulsion was poured into 2 mL of a PVA aqueous solution (5%, w/v). The mixture was emulsified for 4 min using a sonicator operating at 200 W. To allow NP formation, the emulsion was stirred for 4 h on a magnetic stir plate at room temperature. Nanoparticles were recovered by centrifugation at 12,000 rpm for 45min at 4°C for removal of the organic solvent and hardening of the NPs. The NPs obtained were suspended in water and again centrifuged (12,000 rpm for 60 min). The process was repeated three times, and finally, the NPs were prefrozen at−80ºC overnight then were freeze-dried (Four Ring Fury Inc, Beijing, China) for 24 h to obtain the powdered form of NPs. Likewise, EGCG-NPs were prepared and stored at 4°C under anhydrous conditions until it was used for further studies (at least 2 months). Neil Red-NPs were also prepared using an oil-in-water emulsion solvent evaporation technique as previously described. PLGA (10mg) and Neil Red (10 ug) were added to DCM (1 mL) to form the organic phase. ddH2O was used instead of EGCG as the internal aqueous phase [10].

8. **Drug profile**

Epigallocatechin Gallate (EGCG)

Chemical name: (-)-epigallocatechin-3-gallate

IUPACname:(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl 3,4,5-trihydroxybenzoate

Molecular Formula: $C_{22}H_{18}O_{11}$ [12]

Approximate Molecular weight: 458.372gmol-1

Source: Major catechin of camellia sinensis leaves.[11]

9. **Therapeutic effect of EGCG**

1. Anti proliferative role.
2. Cell-cycle modulation.
3. Antioxidant activity.
4. Interference with intracellular signalling cascades
5. Induction of apoptosis [13].

10. **Drug targeting in cancer prevention and chemotherapy**

Typically, cancer therapies involve the systemic administration of drugs into the body or its oral uptake, both of which can damage healthy tissues by significant off-target accumulation and thus, generate serious side effects. Off-target accumulation limits the dosage that can be administered. To overcome this limitation, various targeting strategies are being investigated [14].

Newly developed anticancer drugs may not be therapeutically useful due to poor water-solubility and poor or non-selective distribution of the drug to site of action. A significant amount of work has been done in developing polymeric tumour-targeted NPDDS for anticancer drugs and promising results were reported with improved solubility and better therapeutic efficacy with selective distribution [15].

FUTURE DIRECTIONS

The cost of applying nanotechnology is a major limitation and, for that reason, it is important to lower the cost/benefit for the application of nanocarriers as drug delivery systems for prevention and therapeutic purposes. In this

context, lipid nanocarriers seem to be very promising since they are inexpensive and easy to scale up. These types of nanocarriers showed impressive results in terms of loading efficiency, which is essential to reduce the costs and the toxicity associated with the excipients. The high encapsulation efficiency obtained is due to the ability of this hydrophilic compound to complex with the lipids. These recent advances in EGCG nano delivery systems reinforced the importance of nanotechnology to improve the chemoprevention and therapeutic effects of EGCG, holding a great promise for future clinical applications [16,17].

CONCLUSION

PLGA nanoparticle systems can also carry drugs at the same time. This can make the treatment work better by providing an effect. However, there are still challenges to overcome. These include making quantities of nanoparticles keeping them stable and getting approval for use in people. PLGA nanoparticle systems seem to be one of the options for treating breast cancer. As technology improves these systems will likely become safer, more effective and more comfortable, for patients. PLGA nanoparticle systems have the capability to simultaneously deliver drugs, potentially enhancing the effectiveness of treatments. Nonetheless, several hurdles remain, such as producing sufficient quantities of nanoparticles, ensuring their stability, and obtaining regulatory approval for human use. These systems are considered a promising option for breast cancer treatment. As technological advancements continue, it is anticipated that these systems will become safer, more efficient, and more comfortable for patients.

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