World Journal of Pharmaceutical and Life Sciences

Impact Factor: 8.21 www.wjpls.org Coden USA: WJPLA7

A REVIEW ON CUBOSOMES FOR TARGETED THERAPY IN TRIPLE-NEGATIVE BREAST CANCER AND OPTIMIZING THROUGH QBD

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DOI: https://doi.org/10.5281/zenodo.22159645

How to cite this Article: Muzahidul Islam Akanda[1], Prof. Kumaraswamy Gandla[2]*. (2026). A Review On Cubosomes For Targeted Therapy In Triple-Negative Breast Cancer And Optimizing Through Qbd. World Journal of Pharmaceutical and Life Sciences, 12(9), 6–11.

Article Received on 14/07/2026 **Article Revised on 04/08/2026** **Article Published on 01/09/2026**

INTRODUCTION

Triple-Negative Breast Cancer, commonly abbreviated as TNBC, is a distinctive form of breast cancer that lacks three critical receptors: estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2) as shown in **Fig 1**. These receptors are typically involved in the growth and spread of most breast cancers, and their absence in TNBC means that common hormonal and targeted therapies are ineffective. TNBC.[1-3] represents roughly 10% to 20% of all breast cancer diagnoses and is known for its particular aggressiveness and tendency to affect younger women compared to other breast cancer types.

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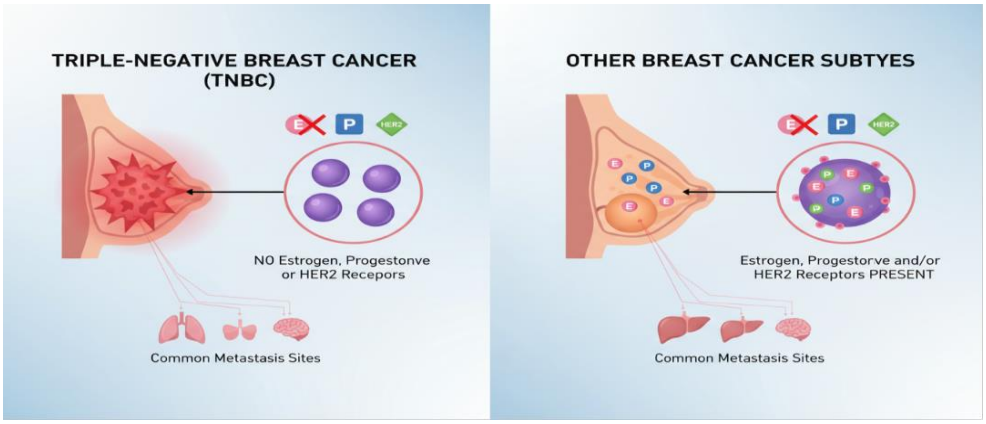

Fig. 1: A breast cross-section with labelled cancer cells, highlighting the absence of estrogen, progesterone, and HER2 receptors in TNBC compared to other subtypes.

From a biological standpoint, TNBC is marked by its rapid cell growth and high tumour grade. Unlike other breast cancers that might develop slowly over time, TNBC tumours often grow and progress quickly, leading to earlier detection but also a higher risk of metastasis. TNBC is also heterogeneous, meaning it encompasses a variety of subtypes at the molecular level. These subtypes can include basal-like, mesenchymal, and immunomodulatory cancers, each with unique genetic and cellular features. This heterogeneity plays a role in the disease's behavior and in the patient's response to various treatments3.[4-7]

Several risk factors are associated with a higher likelihood of developing TNBC. Ethnic background also plays a role—African American and Hispanic women face a higher risk, as do women with limited access to healthcare resources. Genetics are crucial; mutations in the BRCA1 gene, in particular, are strongly correlated with TNBC. In fact, women with BRCA1 mutations are far more likely to develop this subtype than other forms of breast cancer. Additional risk factors include a family history of breast or ovarian cancer, obesity, and certain reproductive or lifestyle factors such as not having children or having a first child at a later age.

TNBC shares many symptoms with other breast cancers but often presents as a rapidly growing lump in the breast or underarm. Other warning signs include noticeable changes in breast size, shape, or contour; skin changes such as thickening, dimpling, or redness; and unusual nipple discharge or inversion. Because TNBC tumors tend to be more aggressive, symptoms can develop and worsen over a relatively short period, prompting quicker medical attention.

The diagnostic process for TNBC starts with imaging studies like mammography, breast ultrasound, and sometimes magnetic resonance imaging (MRI) to visualize the tumour and surrounding tissues as shown in **Fig 2**. If a suspicious mass is detected, a biopsy is performed to obtain a tissue sample for microscopic examination.[8] The key step in identifying TNBC is determining the absence of ER, PR, and HER2 through immunohistochemistry and related tests. For many patients, especially those with a strong family history or diagnosis at a young age, genetic testing for BRCA and other gene mutations is recommended to guide treatment decisions and assess risk for relatives.

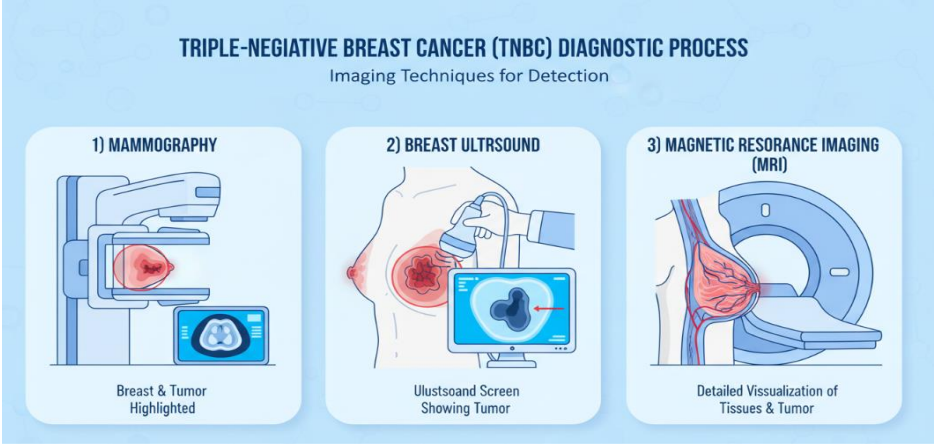

Fig 2: The diagnostic process for Triple-Negative Breast Cancer (TNBC) using mammography, breast ultrasound, and magnetic resonance imaging (MRI).

Treating TNBC requires a multi-pronged approach due to its aggressive and unresponsive nature to standard hormone or HER2-targeted therapies. Surgery is often the first major intervention, involving either a lumpectomy (removal of the tumor and some surrounding tissue) or a mastectomy (removal of the entire breast), depending on the size and spread of the cancer as shown in **Fig 3**. Chemotherapy is a cornerstone of TNBC treatment and can be administered before surgery (neoadjuvant) to shrink the tumor or after surgery (adjuvant) to destroy any remaining cancer cells.[9-11] TNBC is often more sensitive to chemotherapy than other subtypes, leading to higher rates of complete response in some cases.

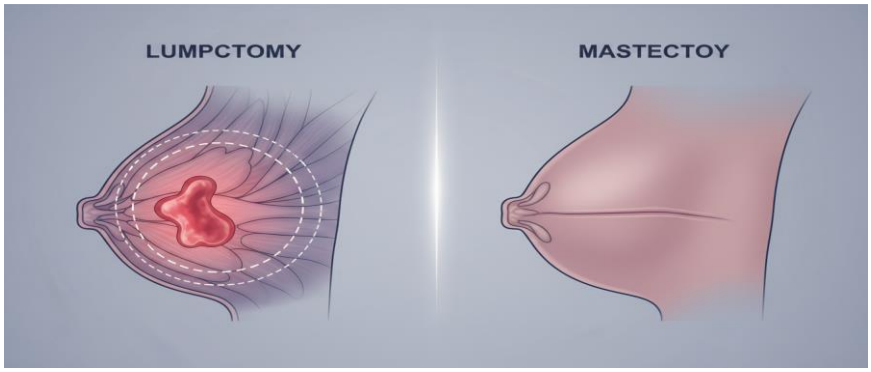

Fig. 3: Difference between a lumpectomy (removal of the tumour and some surrounding tissue) and a mastectomy (removal of the entire breast).

Radiation therapy may be used following surgery to reduce the risk of the cancer returning in the same area. In recent years, targeted therapies have emerged for certain TNBC patients.[12,13] For example, PARP inhibitors like olaparib are approved for TNBC patients with BRCA mutations, exploiting the cancer's defective DNA repair mechanisms. Immunotherapy, such as PD-1/PD-L1 inhibitors like pembrolizumab and atezolizumab, has shown promise in treating advanced or metastatic TNBC, particularly in tumors expressing the PD-L1 protein.

The prognosis for TNBC tends to be less favorable than for other types of breast cancer, mainly due to the cancer's aggressive nature and limited treatment options. There is a higher risk of early recurrence, with most relapses occurring within three years of diagnosis.[14] TNBC is more likely to metastasize to distant organs such as the lungs, liver, and brain.

However, if TNBC is detected early and responds well to chemotherapy, long-term survival is possible. The five-year survival rate for localized TNBC is relatively high, but survival drops significantly for advanced or metastatic disease.

Nanocarrier Systems for Breast Cancer Therapy

A range of nanocarrier systems have been developed and investigated for breast cancer therapy, each offering distinct advantages based on the type of drug and treatment goals.[15,16,17]

Liposomes, which are spherical vesicles with a phospholipid bilayer, are widely used because they can encapsulate both water-soluble and fat-soluble drugs and can be easily modified for targeted delivery.

Solid lipid nanoparticles (SLNs) provide excellent physical stability and controlled release for lipophilic drugs, making them suitable for sustained drug delivery. Polymer-based nanoparticles, such as those made from biodegradable materials like PLGA, offer customizable drug release profiles and can be surface-modified for enhanced targeting of cancer cells.

Cubosomes, with their unique cubic crystalline structure, are gaining attention for their ability to encapsulate a wide variety of drugs and provide controlled, sustained release, as well as for their potential to be engineered for targeted delivery.

Other systems such as micelles, dendrimers, and niosomes also play important roles: micelles are particularly effective for solubilizing poorly water-soluble drugs; dendrimers are highly branched structures capable of carrying multiple drug molecules simultaneously; and niosomes, made from non-ionic surfactants, are valued for their stability and versatility. Additionally, metallic nanoparticles like gold and iron oxide are used for both therapeutic and diagnostic purposes, while nanogels and exosomes are emerging as promising carriers due to their biocompatibility and ability to deliver drugs or genetic material efficiently.

The choice of carrier system depends on factors such as the drug's properties, the desired release profile, the route of administration, and the need for targeting specific tumor sites, all of which contribute to more effective and safer breast cancer treatments.

Selection of cubosomes for breast cancer therapy

Cubosomes are advanced nanostructured particles formed from specific lipids that self-assemble into a unique cubic liquid crystalline phase when dispersed in water. Their structure is characterized by a three-dimensional, honeycomb-like network with two separate but continuous regions—one hydrophilic (water-attracting) and one hydrophobic (water-repelling). This internal bicontinuous cubic phase gives cubosomes a large internal surface area and enables them to encapsulate both water-soluble and fat-soluble drugs simultaneously.[18]

Structural Components

Lipid Bilayer Matrix: Forms a three-dimensional bicontinuous cubic structure.

Common lipids include

- Monoolein (Glycerol monooleate, GMO)
- Phytantriol
  - The lipid bilayer separates two non-intersecting aqueous channel networks.

Interconnected Aqueous Channels: Two continuous but independent water channel systems.

- Facilitate encapsulation of
- Hydrophilic drugs
- Proteins
- Peptides
- Nucleic acids

Hydrophobic Regions: Located within the lipid bilayer.

- Suitable for incorporation of poorly water-soluble drugs.

Polymeric Stabilizer: Prevents aggregation of cubosomes.

- Common stabilizers
- Poloxamer 407 (Pluronic® F127)
- Tween 80
- Adsorbs onto the particle surface.

The structure of cubosomes is especially advantageous for drug delivery. The lipid bilayer forms a matrix with interconnected channels, creating numerous storage spaces for drug molecules.[19,20] These channels provide a protective environment that shields sensitive drugs from degradation and allows for controlled, sustained drug release over time. The unique cubic structure also allows for high drug-loading capacity, which is essential in delivering effective doses of anticancer agents.

Types of Cubic Phases Found in Cubosomes

Three bicontinuous cubic phases are commonly observed:

- **Primitive cubic (Im3m)**
  - Straight interconnected channels.
  - Lower membrane curvature.
- **Double Diamond (Pn3m)**
  - Most commonly formed by monoolein-based cubosomes.
  - Excellent drug-loading capability.
- **Gyroid (Ia3d)**
  - Highly interconnected and complex channel network.
  - Offers efficient diffusion pathways.

Advantages of the Cubosome Structure

- High internal surface area (up to ~400 m^2/g)
- Large drug-loading capacity
- Simultaneous encapsulation of hydrophilic and hydrophobic drugs
- Controlled and sustained drug release
- High physical stability
- Bio adhesive properties
- Protection of sensitive biomolecules
- Enhanced permeability and bioavailability

Correlation Between Cubosomes, Triple-Negative Breast Cancer, and Quality by Design

The successful development of cubosomal formulations for TNBC requires systematic optimization because multiple formulation and process variables significantly influence the final product quality. This necessity has led to the application of the **Quality by Design (QbD)** paradigm, a scientific and risk-based pharmaceutical development approach advocated by the International Council for Harmonisation (ICH).[21-24]

Within the QbD framework, the process begins by defining the **Quality Target Product Profile (QTPP)**, which specifies the intended therapeutic performance of the cubosomal formulation, including dosage form, route of administration, drug release profile, stability, and targeting capability. From the QTPP, the **Critical Quality Attributes (CQAs)** are identified, including particle size, polydispersity index (PDI), zeta potential, entrapment efficiency, drug loading, cubic phase integrity, in vitro drug release, physical stability, and sterility.[25]

Subsequently, **Critical Material Attributes (CMAs)** such as lipid concentration, stabilizer concentration, drug-to-lipid ratio, lipid type, surfactant concentration, and aqueous phase composition are evaluated alongside **Critical Process Parameters (CPPs)** including homogenization speed, probe sonication time, sonication amplitude, mixing temperature, and cooling conditions. These variables collectively determine the structural characteristics and performance of cubosomes.

Risk assessment tools such as Ishikawa (Fishbone) diagrams and Failure Mode and Effects Analysis (FMEA) are employed to identify variables exerting the greatest influence on the CQAs. The significant variables are then optimized using Design of Experiments (DoE) methodologies, including Box–Behnken Design (BBD), Central Composite Design (CCD), or factorial experimental designs. Statistical models generated through Response Surface Methodology (RSM) establish quantitative relationships between CMAs, CPPs, and CQAs, allowing simultaneous optimization of multiple responses while minimizing experimental runs.

The optimized formulation is validated by comparing experimentally obtained values with model-predicted responses. A successful QbD-based cubosomal formulation typically demonstrates a particle size below 200–250 nm, low PDI (<0.30), high entrapment efficiency (>80%), suitable zeta potential for physical stability, sustained drug release, and excellent storage stability. These optimized characteristics directly contribute to improved tumor targeting, enhanced intracellular drug delivery, increased therapeutic efficacy, and reduced systemic toxicity in TNBC treatment.

Thus, the integration of cubosome nanotechnology with the Quality by Design approach represents a rational and robust strategy for developing next-generation targeted therapeutics against triple-negative breast cancer as shown in **Fig 4**. QbD ensures consistent product quality, process reproducibility, regulatory compliance, and scalability from laboratory development to industrial manufacturing, thereby accelerating the translation of cubosomal drug delivery systems into clinical applications for TNBC management.

Conceptual Correlation

Triple-Negative Breast Cancer (TNBC)

⬇ Therapeutic Challenges

- Lack of molecular targets
- Chemotherapy-associated toxicity
- Multidrug resistance
- Poor drug selectivity

⬇**Cubosome-Based Drug Delivery**

- Bicontinuous cubic nanostructure
- High drug-loading capacity
- Controlled and sustained release
- Passive (EPR) and active targeting
- Improved intracellular uptake

⬇**Quality by Design (QbD)**

- Define QTPP
- Identify CQAs
- Screen CMAs and CPPs
- Risk assessment (FMEA/Ishikawa)
- Optimization using DoE (BBD/CCD)
- Design Space establishment

- Validation and control strategy

↓Optimized Cubosomal Formulation

- Small particle size
- Low PDI
- High entrapment efficiency
- Excellent stability
- Enhanced TNBC targeting
- Improved therapeutic efficacy
- Reduced systemic toxicity.

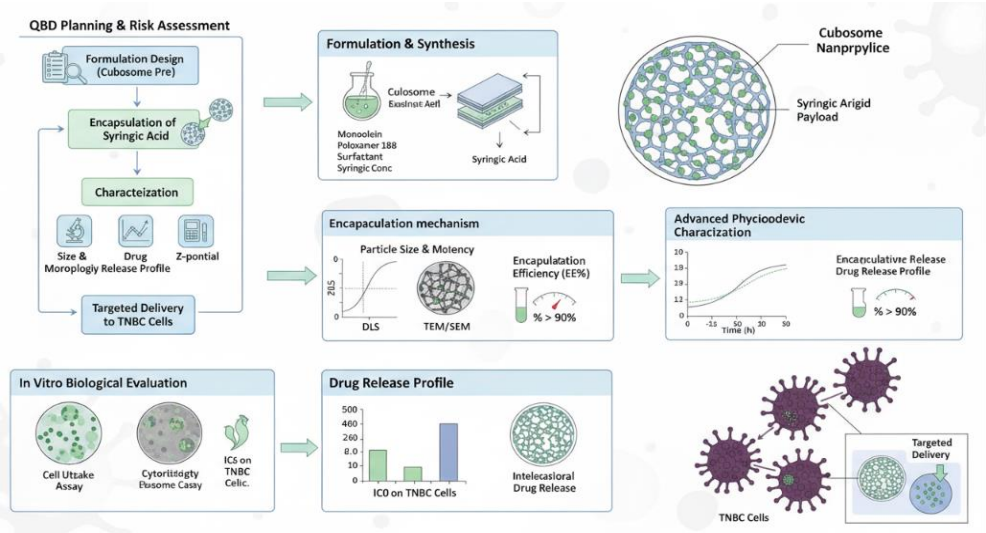

Fig 4: Quality by Design (QbD)-based development process for drug-loaded cubosomes, covering planning, formulation, encapsulation, advanced characterization, biological evaluation, and targeted delivery specific to Triple-Negative Breast Cancer (TNBC).

Advances and Ongoing Research

Research in TNBC is rapidly evolving, with numerous clinical trials underway to find more effective treatments. Immunotherapy has become a cornerstone for a subset of patients and continues to be explored for broader use. PARP inhibitors are revolutionizing care for those with BRCA mutations. Other investigational approaches include antibody-drug conjugates, new small-molecule drugs targeting specific genetic changes, and experimental vaccine therapies designed to stimulate the body's immune response against the cancer. Personalized medicine, where treatments are tailored to the genetic and molecular profile of each tumor, is an area of major advancement for TNBC research.

Living with TNBC can be emotionally and physically challenging. Comprehensive care involves not just medical treatment but also psychological support, nutritional counseling, and physical rehabilitation. Survivorship programs help patients cope with treatment side effects and adjust to life after cancer. Regular follow-up is essential for early detection of recurrence or secondary cancers, and genetic counseling is especially important for patients with BRCA or other high-risk mutations to inform family members about their own cancer risks.

CONCLUSION

Triple-Negative Breast Cancer is a complex and aggressive disease that requires prompt, aggressive treatment and ongoing research for better solutions. While the prognosis is generally less favorable than other breast cancer types, advances in chemotherapy, targeted therapy, and immunotherapy are gradually improving outcomes. Early diagnosis, genetic testing, and comprehensive support are key elements in managing TNBC and improving the quality of life for those affected.

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