RESEARCH PAPER

EMERGING ROLE OF ULTRADEFORMABLE NANOVESICLES IN TARGETED BREAST CANCER TREATMENT

Sarika S. Suryawanshi[1], Saloni S. Chavan[1*], Suvarna S. Patil[2], Ganesh S. Nagargoje[3], Lalita S. Nemade[4], Pratiksha P. Nikam[4], Pranali P. Patil[5], Pramod B. Patil[6], Sachin S. Mali[6], Hemalata S. Dol[7]

[1]Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, India
[SSS: sarikasuryawanshi@amcoph.org]
[2]Department of Pharmacology, Ashokrao Mane Institute of Pharmaceutical science and Research, Save, India
[3]Department of Quality assurance, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, India
[4]Department of Pharmaceutics, Govindrao Nikam College of Pharmacy, Sawarde, India
[5]Department of Pharmaceutical Chemistry, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, Kolhapur, India
[6]Bharati Vidyapeeth College of Pharmacy, Kolhapur, Maharashtra, India
Email id: pramodbpatil24@gmail.com, sachinmali143@gmail.com
[7]Department of Pharmaceutics, Krishna Institute of Pharmacy, Krishna Vishwa Vidyapeeth (Deemed to be University), Karad, India

[2*]**Corresponding Author:** Saloni Shailesh Chavan, Department of Pharmaceutics, Ashokrao Mane College of Pharmacy, Peth-Vadgaon, chavansaloni0709@gmail.com

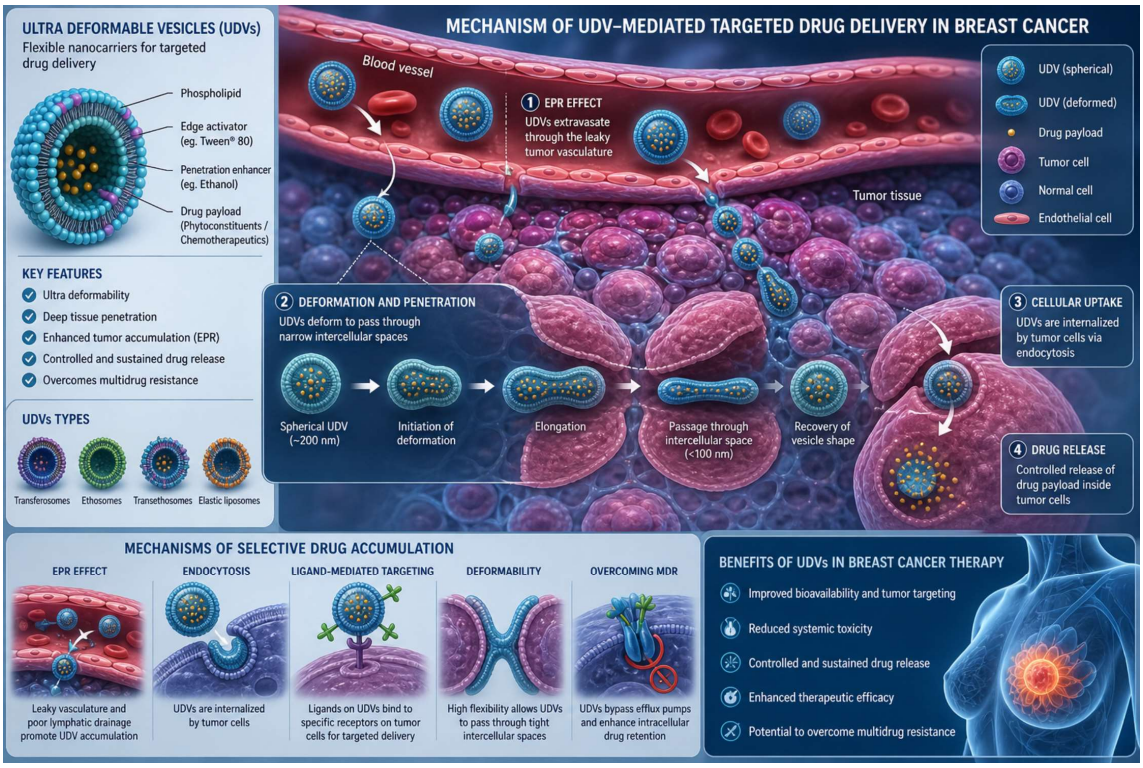
Abstract:

Breast cancer is still one of the major causes of cancer-related deaths in women worldwide, mainly due to tumour heterogeneity, poor treatment selectivity, systemic toxicity and development of multi-drug resistance. Conventional therapies such as chemotherapy and targeted therapy are usually hampered by poor bioavailability and inadequate tumour accumulation. In this context, nanotechnology-based drug delivery systems became viable alternatives to improve the treatment outcomes. Ultra deformable vesicles (UDVs), such as transferosomes, ethosomes, transethosomes and elastic liposomes, have gained much attention due to their unique flexibility and penetration ability. UDVs are nanocarriers of lipids based on phospholipids, edge activators and penetration enhancers, which are effective in delivering drugs to tumor sites overcoming biological barriers. Mechanisms of selective drug accumulation in breast cancer tissues are based on the enhanced permeability and retention (EPR) effect, cellular endocytosis, ligand-mediated targeting, and special deformability allowing them to pass through small intercellular spaces. Furthermore, these systems offer improved bioavailability, controlled and sustained drug release, and the capability to overcome multidrug resistance. This review describes the pathophysiology of the breast cancer, problems with conventional therapy and the new application of ultradeformable vesicles for targeted drug delivery. The composition, production techniques, mechanisms of action and uses of UDVs in the delivery of phytoconstituents, targeted treatments and chemotherapeutic drugs are also discussed. UDVs, in sum, provide a flexible and promising platform for optimizing the safety and efficacy of breast cancer treatment.

Keywords: Breast cancer, Ultra deformable vesicles, Nanocarriers, Targeted drug delivery, Controlled drug release.

How to cite this article: Suryawanshi SS, Chavan SS, Patil SS, Nagargoje GS, Nemade LS, Nikam PP, Patil PP, Patil PB, Mali SS, Dol HS. Emerging Role of Ultradeformable Nanovesicles in Targeted Breast Cancer Treatment. Int J Drug Deliv Technol. 2026;16(51s): 1515-1530. DOI: 10.25258/ijddt.16.51s.112

Graphical Abstract



Introduction:

However, despite the improvement in early detection and treatment, breast cancer is still one of the most common cancers in women worldwide and a major cause of cancer death. This illness represents a diverse group of tumors with different histological and molecular features. This leads to a range of responses and outcomes with treatments. Current treatment options include surgery, radiation therapy, chemotherapy, hormone therapy and targeted biological agents. Conventional therapeutic modalities, however, suffer from several serious drawbacks, such as low absorption, systemic toxicity, insufficient accumulation in tumors, poor selectivity, and the development of multidrug resistance. To overcome such barriers, nanotechnology-based drug delivery systems have emerged that improve pharmacokinetics, decrease off-target effects, and increase drug targeting. Liposomes, polymeric nanoparticles, micelles, dendrimers and ultradeformable vesicles are nanocarriers with obvious advantages in anticancer medicines delivery. These systems can encapsulate both hydrophilic and hydrophobic drugs and protect therapeutic cargo from premature degradation and allow for site-specific and controlled release at tumor sites. The enhanced permeability and retention (EPR) effect, which is characterized by leaky tumor vasculature and poor lymphatic drainage [1], enables preferential accumulation of nanosized

carriers in malignant tissues. Among the nanocarriers, the ultradeformable vesicles (UDVs) have attracted a great attention recently due to their unique structural and functional properties. Ultradeformable vesicles, such as transfersomes, ethosomes, transethosomes, elastic liposomes and invasomes are flexible lipid nanocarriers, which are designed to overcome biological barriers that limit efficacy and penetration of conventional formulations. These vesicles are designed to give flexibility and malleability to the membrane by incorporating edge activators (such as surfactants) or penetration enhancers (such as ethanol, terpenes) into a phospholipid bilayer [2]. UDVs possess the ability to overcome physical barriers, increase permeability into tissues, and facilitate targeted drug delivery owing to their ability to change their shape and pass through tight intercellular junctions. It plays a critical role in the treatment of breast cancer tumors owing to the fact that such tumors may not be easy to target on account of the complexity of the tumor and lack of vasculature.[3]. These promising traits have resulted in the growing focus on the use of ultradefromable vesicles in improving the efficacy and distribution of cancer drugs in the treatment of breast cancer. UDVs are highly suitable for application in cancer nanomedicine owing to their potential to increase the delivery of drugs to the tumor sites and avoid resistance to drugs.

2. Breast Cancer: Pathophysiology and Therapeutic Challenges

Breast cancer, a highly complicated disease, is a result of abnormal growth in breast tissue cells. The cancer consists of many types of tumors that have different biological and molecular characteristics. Due to this heterogeneity in breast cancer, the diagnosis and therapy of the condition become challenging [4].

2.1 Molecular Subtypes of Breast Cancer:

Breast cancers are further classified into various molecular subtypes based on the presence of HER2 and hormones receptors. TNBC, HER2-positive, Luminal A, and Luminal B are some of the common types. Luminal tumors are generally sensitive to hormone treatment and are positive for estrogen and/or progesterone receptors. Target drugs for HER2 are employed for treating HER2-positive breast cancer. Unlike the other types of breast cancer, TNBC is more aggressive, negative for the mentioned receptors, less treatable, and recurs more often [5,6].

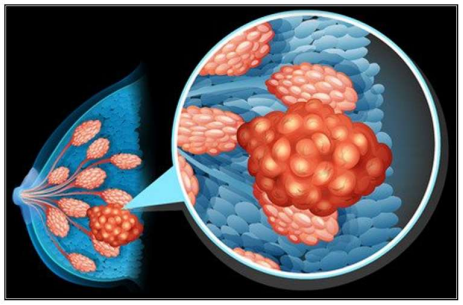


Fig.No. 1.1 Breast cancer

2.2 Tumor Microenvironment:

It is important to note that both the development and therapeutic resistance of breast cancer are affected to some degree by the tumor microenvironment. The tumor microenvironment is comprised of blood vessels, fibroblasts, immune cells, cancer

cells, and extracellular matrix. An acidic environment, excess extracellular matrix within the tumor, malformed blood vessels, and low amounts of oxygen prevent effective delivery of drugs [7,8].

2.3 Drug Resistance and Systemic Toxicity:

Resistance to targeted drugs and chemotherapy is another problem associated with breast cancer treatment. The cancer cells can develop resistance through various mechanisms, including enhanced drug efflux, mutation, and altered biological pathways [9]. Moreover, conventional anticancer drugs can negatively impact healthy tissues and produce serious side effects, such as gastrointestinal toxicity, bone marrow suppression, and cardiotoxicity. Conventional anticancer drugs are also non-tumor-specific. The dose and duration of treatment are often limited by these side effects [10].

2.4 Barriers to Effective Drug Delivery:

Due to the density of the tumor tissue, high pressure of the interstitial fluid, and poor vascularization, it is difficult to administer anticancer drugs to breast cancer tumors. These factors impair the effectiveness of treatment due to the limited diffusion of medications into the tumor tissue [11]. Permeability and retention enhancement (EPR) make it possible for drug carriers at the nanometer scale to accumulate within tumor sites, but the mechanism is not uniform and varies among individuals [12]. Consequently, new strategies need to be developed to surpass these limitations.

3. Ultradeformable Vesicles: An Overview

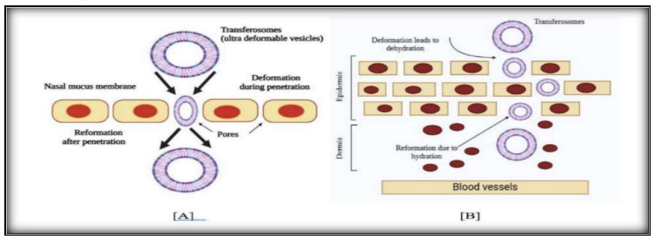


Fig.No. 3.1 Penetration of UDV through skin layers

The development of sophisticated lipid nanocarriers known as ultradeformable vesicles (UDVs) was done specifically to surpass the limitations of conventional liposomes. The ability of UDVs to deform and traverse biological membranes without losing their structure is attributed to their greater membrane deformability compared to conventional liposomes [13]. UDVs are suitable for targeted drug delivery owing to this unique feature, especially in cancer therapy, such as breast cancer. The constituents of UDVs normally include phospholipids, ethanol, or agents such as edge activators that help destabilize the lipids of the lipid bilayer. The ability to destabilize and hence increase the deformability and penetrating capability is achieved through these components [14]. UDVs are therefore capable of carrying both hydrophilic and lipophilic anticancer drugs. Transfersomes, ethosomes, transethosomes, and deformable liposomes are some examples of ultradeformable vesicles that have been developed [15]. The edge activators, such as sodium cholate or Tween 80, that add elasticity to the lipid bilayer of the vesicle are responsible for defining the transfersomes. The presence of ethanol in ethosomes results in enhanced

mobility and penetration through tissues [16]. Some advantages of using UDVs include better drug permeability, higher bioavailability, minimized toxicity effects, and controlled drug release. UDVs are suitable nanovehicles for the delivery of anticancer drugs due to their ability to increase the accumulation of drugs in tumor cells without affecting normal body tissues.

4. Types of Ultradeformable Vesicles Used in Breast Cancer Therapy

The numerous types of altered liposome carriers with different compositions and enhanced methods of penetrating into cells are called ultra-deformable vesicles (UDVs). Concerning the delivery of anticancer drugs for breast cancer treatment, each type has its advantages.

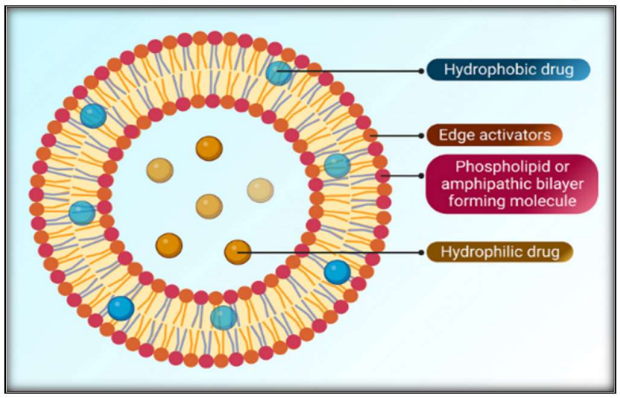


Fig.No.4.1 Structure of Transferosome

4.1 Transfersomes:

The first kind of ultradeformable vesicles are referred to as transfersomes. These are made up of lipids as well as an edge activator such as sodium cholate, Tween 80, or Span 80 [17]. However, transfersomes have the ability to squeeze through the narrow spaces between cells which are considerably smaller in size compared to the transfersome particles without rupturing thanks to their high deformability [18]. Transfersomes have been used for delivering drugs like doxorubicin, tamoxifen, and paclitaxel for treatment of breast cancer, so that they could penetrate better inside tumors and minimize systemic toxicity [19].

4.2 Ethosomes:

The ethosome is an example of lipid-based carrier systems with a high content of ethanol (20-45%) that enables improved tissue permeation and increased membrane fluidity. Ethanol facilitates greater tissue penetration by disrupting the lipid packing in cell membranes. [20,21] Ethosomes have been explored for improving the delivery of plant constituents such as resveratrol and curcumin, as well as chemotherapy agents, with the aim of enhancing their cytotoxic effects against cancer cells, particularly breast cancer cells. Their improved ability to penetrate enhances drug bioavailability and efficacy.

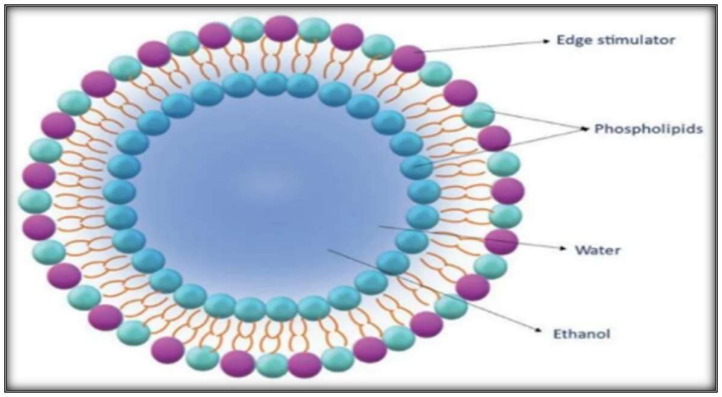


Fig.No. 4.2 Structure of Trans ethosomes

4.3 Transethosomes:

Transethosomes have incorporated the advantages of both ethosomes and transfersomes. Transethosomes exhibit increased flexibility and penetrating power compared to either formulation alone, since the transethosomes comprise phospholipids, ethanol, and edge activators. Transethosomes deliver drugs more efficiently by virtue of its two-stage action (fluidization through ethanol + elasticity via surfactants). The efficacy of these carriers for delivering anticancer agents was shown in breast cancer model systems [22].

4.4 Deformable Liposomes (Elastic Liposomes):

Elastic liposomes are those liposomes modified with softening agents that make their membranes more flexible. [17] Although similar to transferosomes, they do not need to have high concentrations of conventional edge activators. They reduce premature release of drugs and improve permeation. Elastic liposomes have been applied in the delivery of chemotherapeutic agents for breast cancer with improved pharmacokinetic profiles and reduced side effects.[18]

Table No. 1 Classification of UDV on the basis of composition

Category	Penetration enhancers	Example	Mechanism	Application in breast cancer
Surfactant based	Edge activators	Transferosomes	Increase membrane elasticity	Transdermal chemotherapy
Alcohol based	Ethanol	Ethosomes	Fluidizes lipid bilayer	Improved drug permeation
Alcohol + surfactant	Ethanol + EA	Transethosomes	Dual mechanism	Enhanced tumor targeting
Terpene based	Menthol, limonene	Invasomes	Lipid disruption	Herbal drug delivery

Table No. 2 UDV classified according to route of administration

Route	Type of udv used	Suitable drugs	Breast cancer application
Topical	Transferosomes	Doxorubicin	Localized breast tumors
Transdermal	Ethosomes	Paclitaxel	Sustained drug delivery
Systemic	PEGylated UDVs	Methotrexate	Circulating tumor targeting
Intratumoral	Targeted UDVs	SiRNA	HER2- positive cancers

5. Composition and Structural Components of Ultradeformable Vesicles

Certain liposome-based nanostructures, named ultradeformable vesicles (UDVs), are created to be highly deformable with enhanced penetration capabilities. The carefully selected structures provide unique physicochemical properties that govern their deformability, stability, drug-loading ability, and biological activity during the delivery of chemotherapeutic agents for treating breast cancer.

5.1 Phospholipids (Bilayer Forming Agents):

The primary components making up ultradisperse liposomes include phospholipids. Phospholipids like soy phosphatides, egg phosphatides, and phosphatidylcholine (PC) are often used [23]. In aqueous solution, phospholipids form a bilayer structure because they are amphiphilic molecules, and thus give rise to liposomes that contain: hydrophilic drugs (in the aqueous core), lipophilic drugs (within the lipid bilayer). The phospholipids provide biocompatibility, biodegradation, and low immunogenicity for breast cancer therapy, which are essential for safe systemic administration [24].

5.2 Edge Activators (Surfactants):

Edge activators (EAs), which are monomeric surfactants, are used in the phospholipid bilayer to enhance deformability and elasticity of the membrane. Examples include: Tween 80, Span 80, Sodium cholate, Sodium deoxycholate. Through decreasing the interfacial tension, such surfactants destabilize the phospholipid bilayer and make the liposome more deformable to traverse through pores narrower than its size. The amount of edge activator plays an important role:

- Low amount = insufficient deformability
- High amount = vesicle rupture or drug release

In breast cancer studies, the ideal dose of EA leads to a remarkable increase in tumor formation and drug delivery [25].

5.3 Ethanol (Penetration Enhancer):

Ethanol forms an integral component of ethosomes and transethosomes. Ethanol enhances permeation and membrane fluidity by: Interrupting lipid packing in biomembranes, Making vesicles more flexible, Enhancing drug solubility. Higher levels of ethanol (20-45%) enhance the uptake and penetration of anticancer drugs. Ethanolic vesicles have been found to be effective in enhancing the cytotoxic effects on breast cancer cells and localized drug delivery [26].

5.4 Cholesterol (Membrane Stabilizer):

Cholesterol is often added for the purpose of stabilizing the lipid bilayer. Cholesterol makes membranes stiffer, prevents drug release and makes vesicles more stable for long periods of time. However, excess cholesterol can reduce deformability. Therefore, it is essential to have a proper balance between both stability and flexibility [24].

5.5 Penetration Enhancers (Optional Additives):

Some ultradeformable liposomes might contain terpenes or other membrane penetration agents, including but not limited to the following examples: Limonene, Menthol, Cineole. These compounds enhance the permeability of drugs through biological membranes and increase membrane fluidity [27].

5.6 Aqueous Phase:

The aqueous interior of the vesicle is made up of an aqueous phase that dissolves the hydrophilic drugs and may consist of phosphate buffer solution or distilled water. The size, stability, and drug entrapment efficacy are dependent on the pH and ionic strength of the aqueous phase [23].

Structural Characteristics of UDVs:

Ultradeformable vesicles have the following structural features: Lipid bilayer, consisting of phospholipids and edge activators, aqueous core,highly flexible membrane structure. Physical and chemical properties include: size: 50–300 nm, highly deformable zeta potential: negative or neutral, good encapsulation capacity. During the treatment of breast cancer, these structural features enhance tumor proliferation, improve drug delivery, and reduce toxicity [25, 28].

Table No.3 Critical physicochemical parameters influencing UDV performance

Parameter	Ideal range	Importance in breast cancer therapy
Particle size	100-300nm	Better tumor accumulation
Zeta potential	±20-30mv	Stability of formulation
Entrapment efficiency	>70%	Effective drug loading
Polydispersity index	<0.3	Uniform vesicle size
Deformability index	High	Enhanced penetration ability

6. Preparation methods of the UDV:[29]

6.1 Thin Film Hydration Method:

1. To create a thin layer of vesicles, initially phospholipids and surfactants are dissolved in organic solvents (chloroform-methanol). These organic solvents are then evaporated from such a solution, after which it is heated over the lipid's transition point. The lipid film obtained in such a way is exposed to a vacuum for one full day in order to extract the solvent fully.
2. Then, the synthesized film is hydrated through the addition of the appropriate buffer solution and agitation for 60 hours with a speed of 60 revolutions per minute. The swollen vesicles are formed at room temperature.
3. The vesicles formed are then sonicated for 60 min either at room temperature or at 50 °C by using a bath sonicator so that the vesicle size can be reduced. Vesicles are mechanically extruded 200 times through the two layers of membranes having a thickness of 100 nm each.

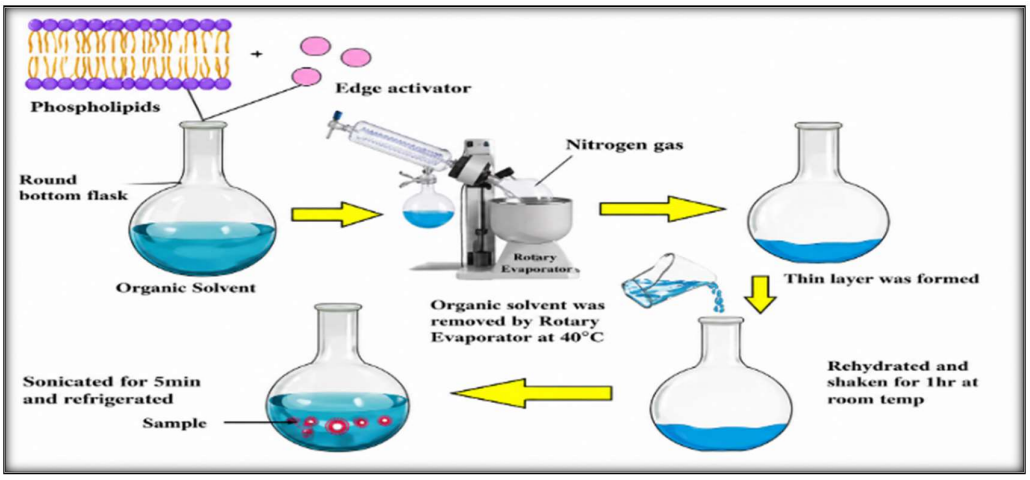


Fig.No. 6.1 Thin film hydration method

6.2 Reverse Phase Evaporation Method:

In this method, the drug and lipid components are dissolved in an organic solvent before adding an aqueous phase to form a water-in-oil (W/O) emulsion. The high-speed homogenization of this W/O emulsion leads to the formation of a system rich in water vesicles, which are later converted to transferosomes.

6.3 Ether Injection Method:

Ether solvent is among those utilized in preparing the drug and lipid solution. The transferosomes are prepared through fast injection of the organic phase into the aqueous medium at high-speed homogenization or sonication.

6.4 Ethanol Injection Method:

The lipids and drugs dissolve in the organic solvent solution with ethanol, just as in the ether injection method. Transferosomes formation occurs due to the rapid injection of the organic phase into aqueous medium under high-speed homogenization or sonication.

7. Mechanism of Drug Delivery of Ultradeformable Vesicles in Breast Cancer

With various coordinated approaches, including enhanced penetration, passive tumor targeting, cellular uptake, and drug release control, ultradeformable vesicles (UDVs) enhance breast cancer treatment. The traditional method of delivering drugs is restricted by biological barriers that can be overcome by ultradeformable vesicles because of their increased flexibility and size on the nanoscale level.

7.1 Deformability-Driven Penetration:

The unique feature of the ultradeformable vesicle is its capacity to stretch and squeeze through channels smaller than their diameter while retaining intact the integrity of their membranes. This feature of UDV is primarily due to the phospholipid bilayer membrane's response to ethanol or edge activators. The UDVs cross biological barriers and small intercellular spaces under osmotic or hydration gradients. This property facilitates drug delivery into breast cancer tissues and ensures deep tissue penetration [30, 31].

7.2 Enhanced Permeability and Retention (EPR) Effect:

Abnormalities in the vascular system of breast cancer tumors include:Permeable blood vessels, Loose junctions between endothelial cells, Limited lymphatic

drainage. This is referred to as the Enhanced Permeability and Retention (EPR) effect. UDV nanoparticles of sizes ranging from 50 to 300 nm exhibit high affinity towards tumors because of the above abnormalities. The EPR effect enables UDV for passive targeting. The result is Concentration of drugs in tumor regions, Limited systemic distribution, Elimination of side effects. Such an approach is useful for administering drugs such as doxorubicin and paclitaxel in breast cancer chemotherapy [32].

7.3 Cellular Uptake Mechanisms:

Following accumulation within tumor tissue, ultradeformable vesicles associate with cancerous cells before being taken up by means of endocytosis. Endocytic pathways may involve endocytosis mediated by clathrin, endocytosis mediated by caveolae, fusion of membranes (occasionally). Upon cellular uptake, vesicles undergo drug delivery inside cells, resulting in increased cytotoxicity towards breast cancer cells [33].

7.4 Controlled and Sustained Drug Release:

The sustained drug release is facilitated by bilayer encapsulation, lipid-drug interactions, membrane destabilization. This prolonged release keeps the drugs active inside the tumor for extended durations at therapeutic levels [31].

7.5 Overcoming Multidrug Resistance (MDR):

Multidrug resistance (MDR) poses a significant problem in the treatment of breast cancer. Breast cancer cells usually produce more efflux pumps like the P-glycoprotein (P-gp) transporter, resulting in reduced drug uptake. The UDVs overcome the MDR problem through endocytosis into cells, higher levels of intracellular drug, prevention of drug destruction. These characteristics improve the efficacy of the treatment of breast cancer resistant cells [34].

8. Mechanism of Targeting of Ultradeformable Vesicles in Breast Cancer

Targeted drug delivery forms an important approach in breast cancer treatment to ensure effective treatment and reduce toxicity. The ultradeformable vesicle (UDV) can reach target cells by way of passive targeting, active targeting, and stimulus response targeting. These methods help improve the accumulation of the drug in cancerous tissues and selective cell destruction.

8.1 Passive Targeting via Enhanced Permeability and Retention (EPR) Effect :

Passive targeting is mainly dependent upon the Enhanced Permeability and Retention (EPR) effect, which is a feature that has been noted in solid tumors such as breast cancer. Breast tumors possess: Damaged blood vessels, Larger endothelial spaces (100-800 nm), Inadequate lymph drainage. Since the ultradeformable vesicles have nanoscale dimensions (50-300 nm), they accumulate in tumor tissues without being quickly removed from the body. This leads to higher concentration of drugs locally, lower systemic distribution, better therapeutic ratio. The EPR effect is the cornerstone of nanocarrier-mediated cancer treatment [35,36].

8.2 Active Targeting (Ligand-Mediated Targeting):

Active targeting uses ligand modification of vesicles such that they can interact with highly expressed receptors found in breast cancer cells. Receptors commonly targeted in breast cancer include the HER2 receptor (found in HER2-positive breast cancer), the Estrogen receptor (ER), the Folate receptor,

the Epidermal growth factor receptor (EGFR), the transferrin receptor. The common ligands used for active targeting include monoclonal antibodies (such as trastuzumab for HER2), folate, peptides, aptamers. On binding, the vesicle is internalized via receptor-mediated endocytosis, leading to increased intracellular drug delivery [37]. Active targeting enhances cancer cell specificity, damage minimization to healthy tissues, therapeutic effectiveness.

8.3 Cellular Internalization Mechanisms:

When attached to the surface of the tumor cell, the ultradeformable vesicles undergo internalization via: Clathrin-dependent endocytosis, Caveolae-dependent uptake, Macropinocytosis. As a result, the anticancer drugs get released inside the cell, resulting in increased cytotoxicity [38]

8.4 Stimuli-Responsive Targeting:

Ultradeformable vesicles can be created that will react to tumor-associated stimuli, including pH changes (pH in tumor microenvironment ≈ 6.5), low concentrations of glutathione, overexpression of enzymes, external stimuli (temperature or light). pH-sensitive vesicles deliver medications selectively at lower pH values inside tumors [39].

8.5 Targeting Tumor Microenvironment (TME):

Components of the breast tumor microenvironment include: Cancer-associated fibroblasts, immune cells, extracellular matrix, hypoxic zones. Due to their deformability, UDV can target the deep tumor tissues, which facilitate penetration in dense tumor matrices, hence overcoming the issue of drug diffusion, which has been a hindrance in conventional chemotherapy treatments. [36]

9. Anticancer Agents Delivered Using Ultradeformable Vesicles

Various types of ultradeformable vesicles (UDVs) such as transfersomes, ethosomes, and transethosomes have been extensively researched to deliver anticancer drugs in treating breast cancer. They enhance drug penetration, increase drug bioavailability, increase drug delivery to the tumors, and minimize toxicity. [40,41] The different types of anticancer drugs used in UDV are categorized into the following: [42-54]

Table No. 9.1 Drugs used in the UDVs

Category	Drug/System	Key Outcome
Chemotherapeutic Drugs	Doxorubicin	Increased permeability, targeted delivery, reduced cardiotoxicity
	Paclitaxel	Improved solubility, permeability, and MCF-7 cytotoxicity
	Methotrexate	Better permeability and controlled release
Phytoconstituents	Curcumin	Enhanced stability, bioavailability, and apoptosis
	Resveratrol	Improved bioavailability and cellular uptake
	Quercetin	Enhanced antioxidant and antiproliferative activity
Targeted UDVs	Folate-conjugated vesicles	Targeted folate receptor-positive cancer cells

	HER2-targeted vesicles	Improved HER2-positive breast cancer delivery
	PEGylated vesicles	Extended circulation half-life
Combination Therapy	Doxorubicin + Curcumin	Synergistic cytotoxicity
	Paclitaxel + siRNA	Reduced drug resistance
	Chemotherapy + Phytoconstituent	Enhanced anticancer activity

Future perspective :

The use of ultradeformable vesicles (UDVs) is highly promising in breast cancer therapy; however, issues like stability, large-scale synthesis, regulations, and clinical validation must be overcome. Recent studies have been conducted on the modification of the surfaces of UDVs using ligands including antibodies, peptides, and folic acid to selectively bind to HER2 and estrogen receptors present in breast cancer cells. Further research should involve the design of smart UDVs with stimuli-sensitive drug release capabilities based on tumor conditions such as pH, enzymes, or redox reactions. UDVs could be used in combination treatments through the simultaneous delivery of chemotherapy drugs, siRNA, or biologically active substances, which could lead to increased synergy and overcoming the problem of multidrug resistance associated with triple-negative breast cancer. Personalized delivery nanocarriers for different types of breast cancer could yield better results.

Conclusion:

Ultradeformable vesicles (UDVs) have emerged as a promising nanocarrier system for breast cancer therapy because they overcome many limitations of conventional treatments. Their high deformability and ability to penetrate biological barriers improve drug delivery, bioavailability, targeting efficiency, and reduce toxicity. UDVs enhance anticancer activity through improved cellular uptake, controlled drug release, and the enhanced permeability and retention (EPR) effect. UDVs can encapsulate a wide range of therapeutic agents, including anticancer drugs, nucleic acids, and phytoconstituents, making them suitable for both monotherapy and combination therapy. Recent advances in ligand-based surface modification have further improved their selectivity toward breast cancer cells, particularly triple-negative breast cancer. Despite their significant potential, challenges related to stability, large-scale production, and clinical translation remain. Ongoing research on targeted delivery, stimuli-responsive systems, and personalized nanomedicine is expected to further improve their therapeutic applications. Overall, UDVs represent a highly promising approach for improving breast cancer treatment by enhancing therapeutic efficacy, reducing side effects, and overcoming drug resistance.

FINANCIAL SUPPORT

Funding information Not available

CONFLICTS OF INTEREST

Conflict of Motivation The authors declare no financial or various disputes of interest pertaining to this work.

DATA AVAILABILITY

The paper itself has data that backs up the study's conclusions. The related author will provide you the data if you ask for it.

Dispute Requiring Use of AI-Assisted Technology

There was no AI employed to write or edit the book, and AI techniques were not utilized to change the pictures.

References:

1. Markman JL, Rekechenetskiy A, Holler E, Ljubimova JY. Nanomedicine therapeutic approaches to overcome cancer drug resistance. Advanced Drug Delivery Reviews. 2013;65(13–14):1866–1879.
2. Nair R, Gupta S, Patel V, et al. A review on skin targeted delivery of bioactives as ultradeformable vesicles: overcoming the penetration problem. Journal of Controlled Release. 2013;172(3):811–824.
3. Manca ML, Castangia I, Caddeo C, et al. Curcumin-loaded ultradeformable nanovesicles as a potential delivery system for breast cancer therapy. Colloids and Surfaces B: Biointerfaces. 2018;168:110–119.
4. Polyak K. Heterogeneity in breast cancer. Journal of Clinical Investigation. 2011;121(10):3786–3788.
5. Perou CM, Sørlie T, Eisen MB, van de Rijn M, Jeffrey SS, Rees CA, et al. Molecular portraits of human breast tumours. Nature. 2000;406(6797):747–752.
6. Waks AG, Winer EP. Breast cancer treatment: A review. JAMA. 2019;321(3):288–300.
7. Jain RK. Normalization of tumor vasculature: An emerging concept in antiangiogenic therapy. Science. 2005;307(5706):58–62.
8. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. Nature Medicine. 2013;19(11):1423–1437.
9. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. Nature Reviews Cancer. 2002;2(1):48–58.
10. Minotti G, Menna P, Salvatorelli E, Cairo G, Gianni L. Anthracyclines: molecular advances and pharmacologic developments in antitumor activity and cardiotoxicity. Pharmacological Reviews. 2004;56(2):185–229.
11. Heldin CH, Rubin K, Pietras K, Ostman A. High interstitial fluid pressure an obstacle in cancer therapy. Nature Reviews Cancer. 2004;4(10):806–813.
12. Maeda H, Bharate GY, Daruwalla J. Polymeric drugs for efficient tumor-targeted drug delivery based on the EPR effect. European Journal of Pharmaceutics and Biopharmaceutics. 2009;71(3):409–419.
13. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochimica et Biophysica Acta. 1992;1104(1):226–232.
14. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of lipid vesicles. Journal of Controlled Release. 1995;36(1–2):3–16.
15. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes novel vesicular carriers for enhanced delivery: characterization and skin

penetration properties. Journal of Controlled Release. 2000;65(3):403–418.
16. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International Journal of Nanomedicine. 2015;10:5837–5851.
17. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochim Biophys Acta. 1992;1104(1):226–232.
18. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of lipid vesicles. Journal of Controlled Release. 1995;36(1–2):3–16.
19. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications. International Journal of Nanomedicine. 2006;1(3):297–315..
20. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of Controlled Release. 2000;65(3):403–418.
21. Gupta A, Aggarwal G, Singla S, Arora R. Ethosomes: a review of their structural characteristics, evaluation and medical applications. International Journal of Pharmaceutical Sciences and Research. 2012;3(10):3337–3344.
22. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International Journal of Nanomedicine. 2015;10:5837–5851.
23. Bangham AD, Standish MM, Watkins JC. Diffusion of univalent ions across the lamellae of swollen phospholipids. Journal of Molecular Biology. 1965;13(1):238–252.
24. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications. International Journal of Nanomedicine. 2006;1(3):297–315.
25. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochimica et Biophysica Acta. 1992;1104(1):226–232.
26. Touitou E, Dayan N, Bergelson L, Godin B, Eliaz M. Ethosomes—novel vesicular carriers for enhanced delivery: characterization and skin penetration properties. Journal of Controlled Release. 2000;65(3):403–418.
27. Dragicevic N, Maibach HI. Percutaneous penetration enhancers chemical methods in penetration enhancement. Springer. 2016.
28. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International Journal of Nanomedicine. 2015;10:5837–5851.
29. Vemula P, Sailaja AK. Transferosomes : A novel carrier for drug delivery. Journal of Dermatology and Dermatitis. 2023;8(5):132.

30. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. Biochimica et Biophysica Acta. 1992;1104(1):226–232.
31. Cevc G, Schatzlein A, Blume G. Transdermal drug carriers: basic properties, optimization and transfer efficiency in the case of lipid vesicles. Journal of Controlled Release. 1995;36(1–2):3–16.
32. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. Journal of Controlled Release. 2000;65(1–2):271–284.
33. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications. International Journal of Nanomedicine. 2006;1(3):297–315.
34. Gottesman MM. Mechanisms of cancer drug resistance. Annual Review of Medicine. 2002;53:615–627.
35. Maeda H, Wu J, Sawa T, Matsumura Y, Hori K. Tumor vascular permeability and the EPR effect in macromolecular therapeutics: a review. Journal of Controlled Release. 2000;65(1–2):271–284.
36. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to the transdermal osmotic gradients and hydration force. *Biochimica et Biophysica Acta*. 1992;1104(1):226–232.
37. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nature Reviews Cancer. 2009;9(7):463–475.
38. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications. International Journal of Nanomedicine. 2006;1(3):297–315
39. Bae YH, Park K. Targeted drug delivery to tumors: myths, reality and possibility. Journal of Controlled Release. 2011;153(3):198–205.
40. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praça FG, et al. Development, characterization, and skin delivery studies of related ultradeformable vesicles: transfersomes, ethosomes, and transethosomes. International Journal of Nanomedicine. 2015;10:5837–5851.
41. Cevc G, Blume G. Lipid vesicles penetrate into intact skin owing to transdermal osmotic gradients and hydration force. Biochimica et Biophysica Acta. 1992;1104(1):226–232
42. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications. International Journal of Nanomedicine. 2006;1(3):297–315.
43. Barenholz Y. Doxil®: the first FDA-approved nano-drug: lessons learned. Journal of Controlled Release. 2012;160(2):117–134
44. Wang AZ, Langer R, Farokhzad OC. Nanoparticle delivery of cancer drugs. Annual Review of Medicine. 2012;63:185–198.
45. Shanmugam MK, Rane G, Kanchi MM, Arfuso F, Chinnathambi A, Zayed ME, et al. The multifaceted role of curcumin in cancer prevention and treatment. Molecules. 2015;20(2):2728–2769.
46. Torchilin VP. Recent advances with liposomes as pharmaceutical carriers. Nature Reviews Drug Discovery. 2005;4(2):145–160.

47. Zhou H, Beevers CS, Huang S. The targets of curcumin. Current Drug Targets. 2011;12(3):332–347.
48. Bishayee A. Cancer prevention and treatment with resveratrol. Cancer Prevention Research (Philadelphia). 2009;2(5):409–418.
49. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nature Reviews Cancer. 2009;9(7):463–475.
50. Lu Y, Low PS. Folate-mediated delivery of macromolecular anticancer therapeutic agents. Advanced Drug Delivery Reviews. 2012;64:342–352.
51. Baselga J, Swain SM. Novel anticancer targets: revisiting ERBB2 and discovering ERBB3. Nature Reviews Cancer. 2009;9(7):463–475.
52. Allen TM, Cullis PR. Liposomal drug delivery systems: from concept to clinical applications. Advanced Drug Delivery Reviews. 2013;65(1):36–48
53. Zhang Y, Chan HF, Leong KW. Advanced materials and processing for drug delivery. Advanced Drug Delivery Reviews. 2013;65(1):104–120.
54. Peer D, Karp JM, Hong S, Farokhzad OC, Margalit R, Langer R. Nanocarriers as emerging platforms for cancer therapy. Nature Nanotechnology. 2007;2(12):751–760.