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Formulation & Evaluation of Curcumin – Loaded Niosomes for Breast Cancer Treatment

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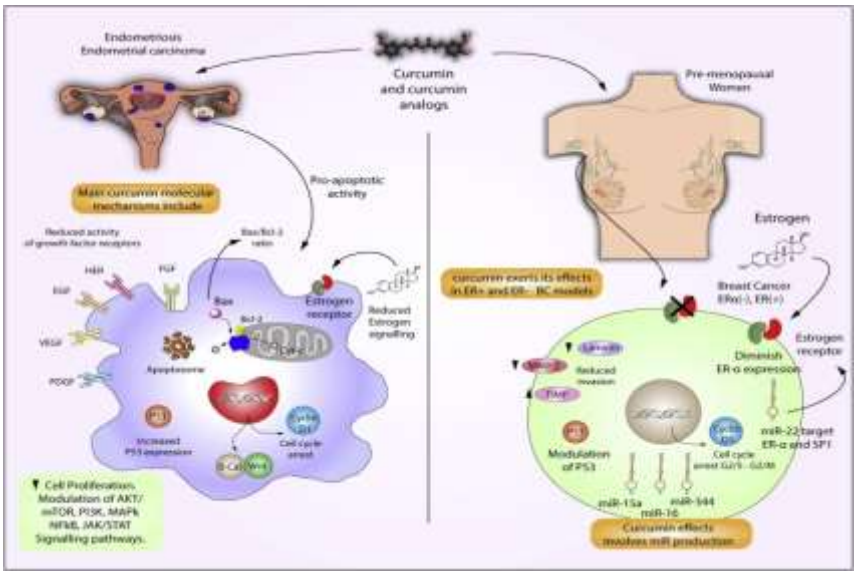
ABSTRACT :

Breast cancer remains the most prevalent malignancy among women worldwide, contributing significantly to cancer-related morbidity and mortality. Conventional chemotherapeutic regimens are often limited by poor solubility of drugs, systemic toxicity, and multidrug resistance, necessitating the development of novel drug delivery approaches.

Curcumin, a bioactive polyphenol derived from Curcuma longa ,exhibits potent anticancer, anti-inflammatory, and antioxidant activities, but its clinical application is hindered by poor aqueous solubility, rapid metabolism, and low bioavailability. Niosomes-non-ionic surfactant-based vesicular carriers—have emerged as a promising nanocarrier system capable of encapsulating both hydrophilic and lipophilic drugs, enhancing stability, bioavailability, and targeted delivery. This review focuses on the formulation strategies, characterization techniques, and therapeutic potential of Curcumin-loaded niosomes for breast cancer management. Methods of preparation such as thin-film hydration, reverse phase evaporation, and microfluidization are discussed along with key evaluation parameters including particle size, zeta potential, entrapment efficiency, in-vitro release, and cytotoxicity studies. Preclinical investigations have demonstrated that curcumin-loaded niosomes improve cellular uptake, induce apoptosis, inhibit tumor proliferation, and minimize off-target toxicity compared to free curcumin. Collectively, these findings highlight the promise of niosomal formulations as an efficient platform for targeted and controlled delivery of curcumin, potentially overcoming major limitations of conventional breast cancer therapy and paving the way for clinical translation.

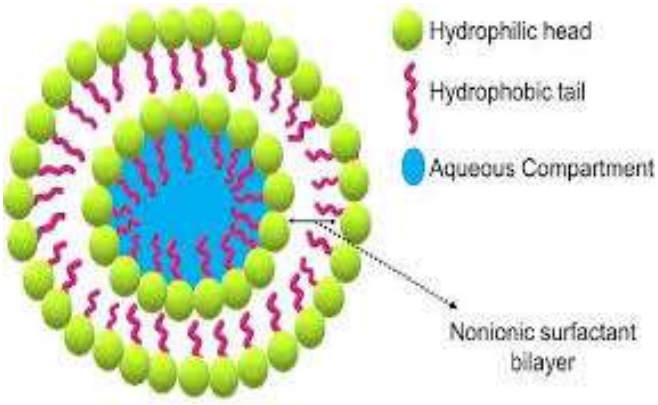
Key words: Curcumin , Niosomes, Breast cancer ,Nanotechnology,Targeted drug .



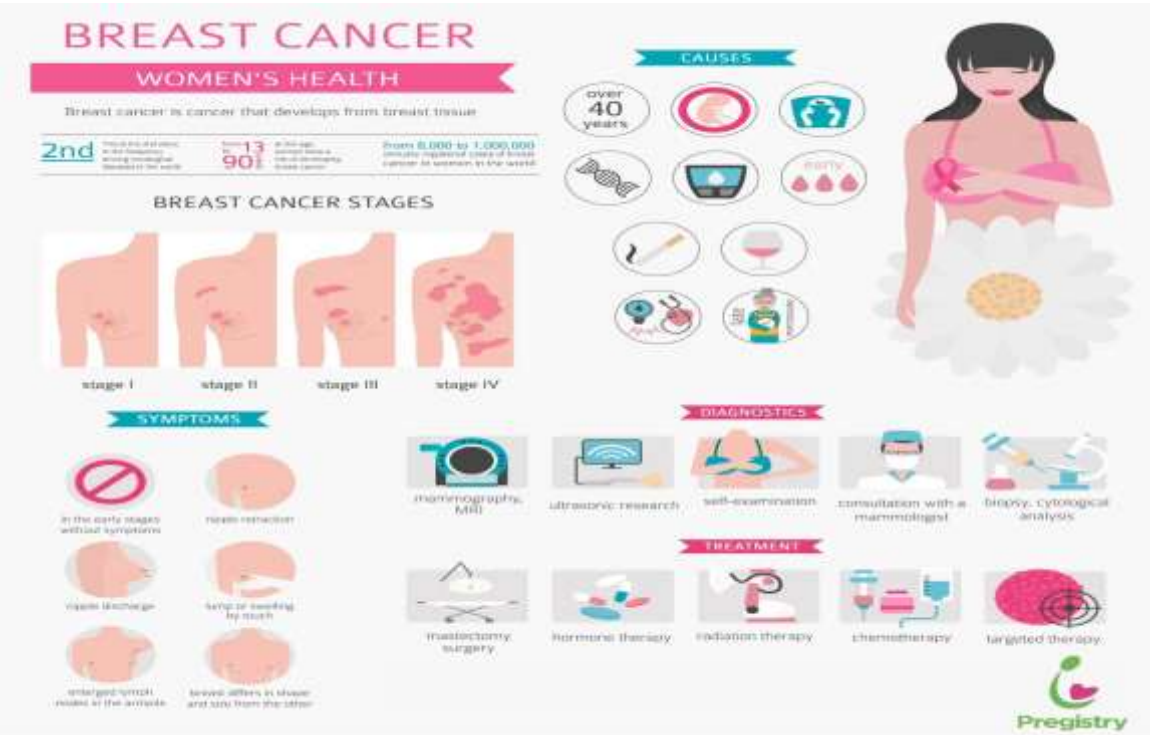
Introduction

Nano-sized vesicular particles, niosomes fall into two categories: small unilamellar vesicles (SUVs), which range in size from 10 to 100 nm, and large unilamellar vesicles (LUVs), which range in size from 100 to 3,000 nm. These vesicles can encapsulate a variety of substances within their core, and their membranes are made up of one or more types of non-ionic surfactants along with cholesterol, which improves structural integrity. Because the surfactants are amphiphilic, meaning they contain both hydrophilic and hydrophobic regions, niosomes can efficiently deliver both hydrophilic and hydrophobic drugs [1]. Additionally, niosomes are very stable, which enables regulated release of chemicals and extended encapsulation. Furthermore,

the safety profile of niosomes is further improved by the use of non-ionic surfactants, which are less toxic and hence appropriate for pharmaceutical uses in drug delivery systems. Numerous techniques, including ether injection, reverse-phase evaporation, thin-film hydration, and sonication, have been used to manufacture niosomes [2]. These techniques usually rely for the use of organic solvents, which may leave traces of these substances in the niosomes. In recent years, the bubble approach has been used to manufacture niosomes without the use of organic solvents. . To create big unilamellar vesicles, this approach is laborious and necessitates particular handling (such as regulating nitrogen flow and evaporation rates). Therefore, in this study, we provide a simple, inexpensive, and environmentally friendly alternative approach for producing niosomes utilizing a ball milling technique.

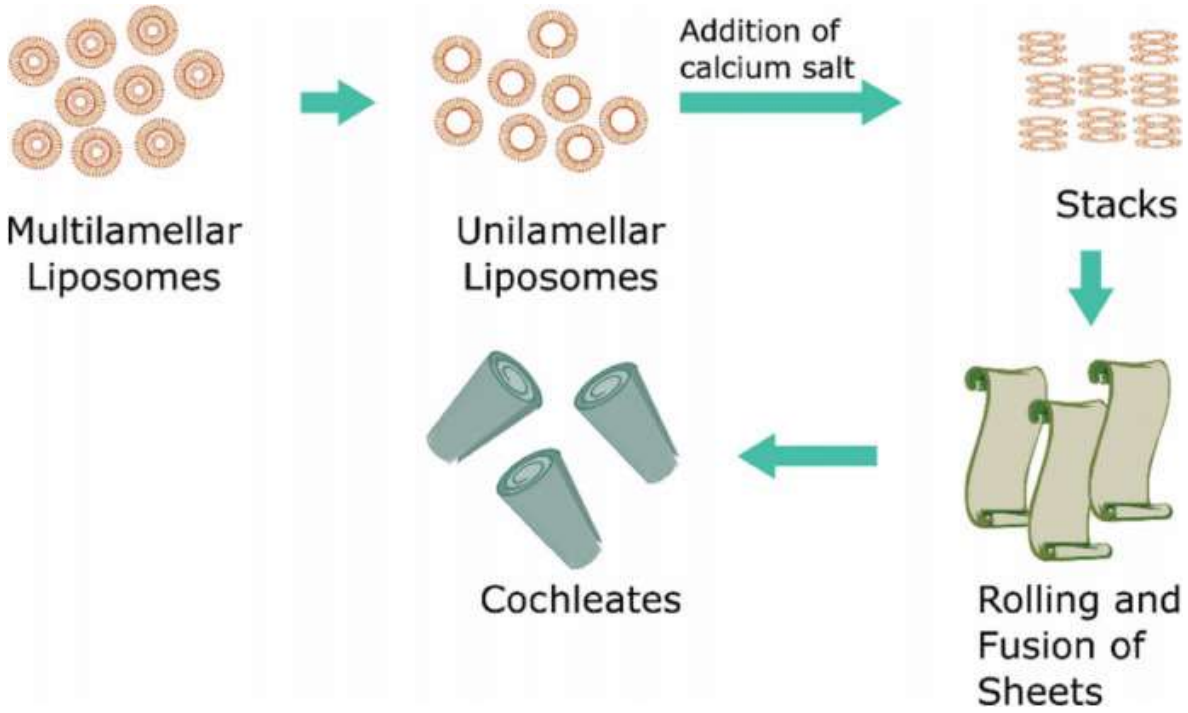


Particularly effective against Ae. aegypti, Culex pipiens (a common vector of Japanese encephalitis), and Anopheles quadrimaculatus (a common vector of malaria) larvae are curcuminoid pigments, particularly curcumin, which is a naturally occurring pigment from Curcuma longa rhizomes. Because it absorbs photons in the 300–500 nm range, with the largest absorption occurring at 420 nm, the blue area of the sunlight spectrum, this pigment has a significant larvicide effect when exposed to sunlight. The repelling qualities and bioactive potential of curcuma essential oils has also been documented in the past on Cx. pipiens, Ae. albopictus, and Ae. aegypti [3]. Along with these qualities, curcuminoids have also been demonstrated to be highly effective medicinal substances with antibacterial, antiseptic, and anti-inflammatory effects [6]. This cutting-edge method of healthcare uses nanoscale tools and materials to identify, cure, and prevent a range of illnesses, such as cancer, neurological problems, cardiovascular diseases, and bacterial survival. Since nanomedicine makes it easier to administer drugs precisely and lessens the side effects that are frequently connected to traditional therapies, it has the potential to completely transform modern medical procedures. Numerous metallic nanoparticles with these special qualities, such as carbon, silica, titanium and zinc oxides, gold, and silver, have been the subject of much research. In particular, gold nanoparticles (AuNPs) are unique among nanoparticle kinds because of their easily changing surfaces, biocompatibility, and adjustable optical properties.



Nanocochelates gel :

The condensation of a tiny negatively charged lipid with divalent cation results in the formation of nanocochleates, which are stable microstructures in the shape of cylindrical cigars that consist of lipid bilayer chains . Phosphatidylserine and calcium are the chief components of nanocochleates shows the basic structure of nanocochleates. The structure of nanocochleate is distinct, composed of a lipid bilayer sheet wrapped up in a stacked or spiralled configuration with tiny or devoid of internal aqueous space . Such arrangement renders shielding to the “encochleated” molecules and protects them from degradation.[5]. Since nanocochleate is made up of solid layers, molecules that are enclosed within the structure are protected even if the structure's outer layer is exposed to enzymes or an unfavorable environment. Because nanocochleates have both hydrophilic and hydrophobic surfaces, they can be used to encapsulate hydrophobic medications like Clofazimine and Amphotericin B as well as amphiphilic medications like Doxorubicin. [8]



Epidiomology and Factor Risk: Breast cancer is a diverse illness with several subtypes that each have their own epidemiological characteristics. Around 15% of all cases identified worldwide are fatal, and breast cancer makes up around one-third of all female cancers. The global distribution of breast cancer is influenced by a complex interaction of lifestyle, environmental, and hereditary factors. While mortality rates are frequently lower because of improved access to early detection and treatment, high-income nations generally have higher incidence rates than low- and middle-income countries [9]. It is significant because as a result of population increase and the adoption of western lifestyles, the absolute number of cases of breast cancer is rising in many emerging nations. Thankfully and predictably, as more women get access to better prevention, early detection, and medical intervention services, the fatality rates will decrease in the future [4]. Regardless of per capita income, breast cancer is the most common cancer diagnosed in women worldwide. 3, 4. An estimated 1.7 million instances of breast cancer are diagnosed globally each year, or around one new case every 18 seconds. 3, 4. Incidence rates, however, differ by almost four times (Fig. 1), with lower incidence reported in lower income locations (27 per 100,000 in Middle Africa) and greater incidence reported in higher income regions (92 per 100,000 in North America). & Age

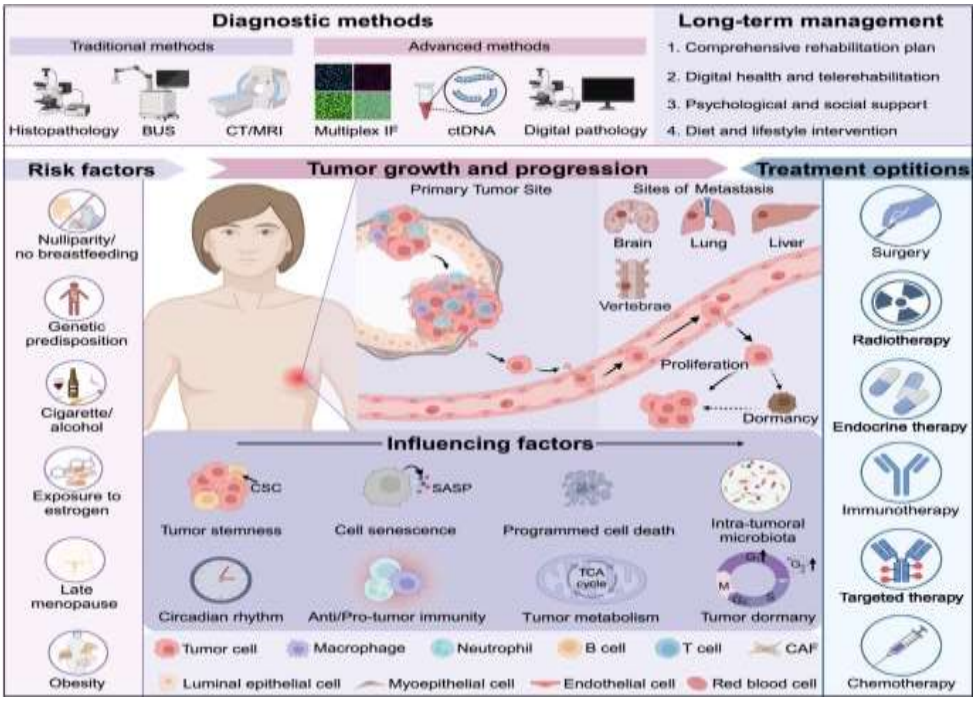
As people age, the incidence and mortality of breast cancer rise proportionately. With a steep decline starting at age 40, this disease peaks globally around age 60. 4, 8 Of course, there are a few outliers. For instance, between the ages of 20 and 44, 20% to 30% of breast cancers are identified in Latin America; this is about twice the rate seen in the combined USA and Canadian registries. 19. Similarly, in Asian and African countries, the average age at diagnosis was between 40 and 50 years old. [20]

Preventing breast cancer

For people who test positive for a BRCA mutation or mutations, interventions are available. The patient should be informed of their options, including any potential long-term impacts and the side effects of each treatment. [10]

Early identification and screening for breast cancer

Early detection of life-threatening disorders is achieved by screening tests. Early disease diagnosis can reduce the likelihood that a disease will manifest later in life and improve outcomes for individuals who already have it. Talking with patients is crucial in order to weigh the possible advantages.



Methods	Advantages	Disadvantages
Mammogram	Mammography is a widely accepted method for breast cancer screening. It's cost-effective and has good image quality.	Discomfort during compression and exposure to low-dose radiation are drawbacks. False positives and negatives can occur.
Ultrasound	Ultrasound is safe, non-invasive, and does not involve ionizing radiation. It's effective in distinguishing between cysts and solid masses.	Its sensitivity/accuracy may vary and is often used as a supplementary tool rather than a stand-alone screening method.
MRI	MRI is highly sensitive, making it practical for women with dense breast tissue or those at high risk. It does not use radiation.	It may produce false positives, leading to unnecessary interventions. The high cost and low availability of MRI can also be limiting factors.
Thermography	Thermography is non-invasive and radiation-free, providing functional information about blood flow and heat patterns.	Its efficacy as a stand-alone screening method is debated. There are issues with interpretation and standardization.

Techniques for Making Niosomes

Method of Thin-Film Hydration (TFH)

A popular and easy preparation technique is thin-film hydration. This process involves dissolving surfactants, cholesterol, and certain additives, including charged molecules, in an organic solvent in a flask with a circular bottom. A rotating vacuum evaporator is then used to extract the organic solvent, leaving a thin layer on the flask's interior wall. The dry film is hydrated above the surfactant's transition temperature (Tc) for a predetermined amount of time while being continuously shaken with an aqueous drug solution. This process creates multilamellar niosomes. [13]

Method of Ether Injection (EIM)

The ether injection method involves dissolving surfactants with additives in diethyl ether and then slowly injecting them through a needle into an aqueous drug solution that is kept at a temperature above the organic solvent's boiling point. A rotary evaporator is used to evaporate the organic solvent. Single-layered vesicles are formed during the vaporization process. [13]

Method of Reverse Phase Evaporation (REV)

This procedure involves dissolving niosomal components in a solution of ether and chloroform, then adding them to the drug-containing aqueous phase. The organic phase is removed by sonicating the resultant mixture to create an emulsion. As the organic solvent evaporates, large unilamellar vesicles are created. [13]

Method of Microfluidization

The submerged jet idea is the foundation of the microfluidization technique. Using this technique, the drug and the fluidized streams of surfactant interact in the interaction chamber's precisely specified microchannels at extremely high speeds. Niosomes occur as a result of the high energy and speed of impact. When it comes to niosome formulation, this approach offers higher reproducibility, unilamellar vesicles, smaller size, and greater uniformity. [13]

Method for Making Nanocochelates: Cochleation Induced by Calcium: Add calcium chloride to the dispersion of niosomes. Nanocochleates are produced when cochleates are induced by calcium ions. [16]

Nanocochelate gel preparation using the hydrogel method The hydrogel method of producing nanocochleates involves the following steps:

First Step: Small unilamellar niosomes or molecule-loaded niosomes with biological significance are suspended. This can be done using common techniques like sonication, microfluidization, and other similar methods.

Step 2: The liposome solution is mixed with polymer A, such as phosphatidyl serine, polyethylene glycol (mol.wt. – 3400–8000), or dextran (mol.wt. – 2, 00,000–5, 00,000).

Step 3: To create an aqueous two-phase polymer system, the niosomes/polymer A solution is mixed with another polymer B, such as polyvinyl pyrrolidone, polyvinyl alcohol, Ficoll (mol.wt – 30,000 – 50,000), and polyvinyl methyl ether (PVMB) (mol.wt – 60,000 – 1,60,000). This could be done mechanically with a syringe pump that is adjusted to the proper rate.

Step 4: To create miniature cochleates, a cation salt solution is added to the two-phase system of steps 3 so that the cation diffuses into polymer B and then into the particles that comprise the liposome/polymer A.

Step 5: Cochleate precipitates are periodically washed with a buffer solution containing a positively charged molecule, particularly a divalent cation, to isolate the cochleate structures and remove the polymer solution.

Trapping method: Encochleation of both hydrophilic and hydrophobic compounds is possible with this approach. It comprises of a niosomes solution formulation that encloses the drug in the aqueous layer of the liposome for hydrophilic drugs or intercalated within the bilayers for hydrophobic drugs. Water could be added to phospholipid powder or water phase could be added to phospholipid film to make niosomes. The addition of calcium to a liposomal suspension drop creates a cochleate assembly.[3]

Step 1: Vortex the fluid for 15 minutes to create niosomes from phospholipids such as phosphatidyl serine.

Step 2: The prepared niosomes are separated from the previously described solution using filtration.

Step 3: The hydrophobic drug is given to the separated niosomes after a capturing solvent, like ethanol or dimethyl sulfoxide, has been applied.

Step 4: Add a calcium chloride solution dropwise to the step 3 solution to precipitate crystalline cochleates.

Step 5: The cochleates are rinsed with a buffer containing calcium to get rid of any leftover solvent. The modified trapping method dissolves dioleoyl phosphatidyl serine (DOPS) in ethanol. After adding calcium chloride (cacl2) and homogenizing it for five minutes at 13,000 rpm, it is stirred for an hour[29].

Niosomes prior to the dialysis technique for cochleates (LC): Tiny cochleates, which are composed of lipids, detergent, a physiologically significant substance, and a cation, are created using this method. The main objective of adding detergent is to disturb the niosomes. The cochleates are created by dialyzing the mixture with a buffer and then adding calcium chloride. The detergent is removed by double dialysis. The following are the steps in this process: [4]

Step 1: An aqueous suspension is created using the lipid detergent combination.

Step 2: Mix polymer A with the suspension made in step 1, such as phosphatidyl serine, dextran, or polyethylene glycol (PEG).

Step 3: Lipid/polymer A, the detergent. A solution containing polymer A is mixed with polymer B, such as polyvinyl pyrrolidone (PVP), polyvinyl alcohol (PVA), and polyvinyl methyl ether (PVME). A two-phase polymer system is formed by the immiscible polymers A and B. Step 4: A cationic moiety solution is added to the two-phase polymer system.

Step 5: Washing the two-phase polymer system[30] removes the polymer.

Large cochleates are produced using the direct calcium (DC) dialysis technique. A calcium chloride solution is dialyzed directly against the lipid and detergent mixture. The following are the steps in this process:

Step 1: Phospholipids and cholesterol are mixed in a 9:1 weight ratio in an extraction buffer.

Step 2: A predefined concentration of API is mixed with a non-ionic detergent and vortexed for five minutes.

Step 3: The clear solution produced in step 2 is dialyzed against three distinct buffers at ambient temperature.

Step 4: Although 3mM Ca2+ is sufficient, the final dialyses are performed in a 6mM Ca2+ solution. DC cochleate is the white calcium phosphor lipid that is produced.

Binary aqueous-aqueous emulsion system: The incompatibility of two-phase systems ofpolymer solutions, both of which are aqueous and immiscible with one other, is the basis for this approach. This approach does not necessitate the use of an organic solvent. It's utilised to make cochleates with a diameter of less than 1000nm. The steps in this procedure are as follows:

Step 1: Niosomes are created using either a high PH or a film technique.

Step 2: Niosomes are combined with a polymer A like Dextran.

Step 3: The dextran/liposome phase is then combined with a non-miscible polymer, such as PEG.

Step 4: Calcium is then added to the step 3 solution, causing Nanocochleates to diffuse softly from one phase to the next. The gel is then rinsed in physiological buffer [31].

EVALUATION:

1. Density: The density of nanocochleates is measured using a gas pycnometer filled with air or helium. The value obtained with air and helium is significantly higher because of the structure's specific surface area and porosity.

2. Determination of particle size: A Malvern analyzer and a laser diffraction technique can be used to determine the mean particle size of niosomes and cochleate dispersion. A temperature of 30±2°C and a detection angle of 900 should be used for this analysis.

3. Determination of molecular weight: Gel permeation chromatography (GPC) can be used to determine the molecular weight of the polymer and its distribution throughout the matrix using a refractive index detector. Entanglement creates polyalkylcynoacrrylate nanocochleates.

According to GPC[32], this is not the rolling up of one or a few big polymer chains, but rather of numerous small oligomeric subunits. [12]
4. Content of drugs: To extract the free medication from the supernatant, the redispersed nanocochleates suspension is centrifuged at 15,000 rpm for 40 minutes at 250°C. Following the proper dilution, ultraviolet UV-Vis spectrophotometry can be used to determine the medicine concentration in the supernatant.

5. Entrapment efficiency: To improve entrapment efficiency (EE), 100L of cochleates are aliquoted into centrifugation tubes. Fill each tube with 60L of PH 9.5 ethylenediamine tetraacetic acid and 1ml of ethanol while vortexing. The absorbance of the solution is measured using the spectroscopic method. [12]

Cochleate-cell interaction: Fluorescent liposomes are created by combining negatively charged lipid with 2% fluorescent lipid. When cochleates make contact with cell membranes through a fluorescent lipid transfer, cell surfaces turn fluorescent when seen under a fluorescent microscope. Area of a particular surface: The specific surface area of freeze-dried nanocochleates can be measured with a sorptometer. The following formula[34] can be used to determine a certain surface: - $A=6/\rho d$

1. Where,

2. A = Specific Area of Surface

3. Density = ρ

4. d is the cochleate's diameter. Surface charge: Surface charge is calculated using the velocity of particles in an electric field. Laser light scattering is used to measure the velocities of nanocochleates.

USE: 1. To treat coronary atherosclerosis and other coronary heart disorders, an Apo-A1 formulation based on nanocochleate was developed[35]. [16]
2. Proteins, peptides, and DNA are transported by nanocochleates in gene transfer therapy and vaccination applications. [16]

3. By stabilizing and preserving a broader range of micronutrients, nanocochleates may improve the nutritious content of processed foods. [16]

4. Without altering the finished product's flavor or odor, nanocochleates can add omega-3 fatty acids to cakes, muffins, pasta, soups, and cookies [35]. [16]

5. One advantage of cochleates is that they increase bactericidal activity[36] and decrease toxicity. [16]

6. Nanocochleates may be able to administer the antifungal medication Amphotericin B parenterally and orally while preserving a higher safety profile and reducing treatment expenses [37]. [16]

7. A US-based company called Bio Delivery Sciences International (BDSI) has created nanocochleates that can be used to more efficiently deliver nutrients like vitamins, omega fatty acids, and lycopene to cells without changing the color or flavor of food, bringing the idea of superfoods closer to reality[38][12].

Discussion :

In the present study , curcumin-loaded niosomes were successfully formulated & characterized to improve the solubility,stability,& anticancer efficacy of curcumin against breast cancer. Curcumin ,despite its proven chemopreventive & chemotherapeutic potential , suffers from poor aqueous solubility,rapid metabolism,& low systemic bioavailability,which limit its clinical utility .Niosomal encapsulation provided an effective approach to overcome these limitations by entrapping the hydrophobic drug within a biocompatible vesicular system.

The optimized niosomal formulation demonstrated a particle size in the nanometer range,with a narrow polydispersity index ,indicating indicating a uniform and homogeneous dispersion suitable for systemic delivery. The zeta potential values were within the range of ±30 mV, suggesting good electrostatic stability and minimal risk of particle aggregation during storage. Entrapment efficiency (EE%) was found to be significantly high, confirming the effective incorporation of curcumin within the non-ionic surfactant bilayer. This is attributed to the hydrophobic nature of curcumin, which readily partitions into the lipid bilayer of the vesicles.

Fourier Transform Infrared (FTIR) spectroscopy and Differential Scanning Calorimetry (DSC) studies confirmed the absence of significant drug–excipient interactions and the successful encapsulation of curcumin in an amorphous or molecularly dispersed state. The in-vitro release studies exhibited a biphasic pattern with an initial burst release followed by sustained release over an extended period, which is desirable for maintaining therapeutic drug levels and reducing dosing frequency.

Cytotoxicity studies against breast cancer cell lines (e.g., MCF-7, MDA-MB-231) revealed that curcumin-loaded niosomes exhibited enhanced antiproliferative activity compared to free curcumin. The improved efficacy can be explained by the increased cellular uptake of nano-sized vesicles through endocytosis and the prolonged intracellular retention of curcumin. Furthermore, apoptosis assays confirmed the ability of curcumin-loaded niosomes to induce cell death via intrinsic apoptotic pathways, evidenced by upregulation of pro-apoptotic markers(Bax, caspase-3) and downregulation of anti-apoptotic proteins (Bcl-2).Overall, the findings indicate that niosomal delivery of curcumin successfully addresses key limitations of conventional curcumin therapy by enhancing solubility, bioavailability, and targeted cytotoxicity, while potentially minimizing systemic toxicity. These results are consistent with previously reported studies and highlight the promise of niosomal systems as a platform for effective breast cancer therapy. However, further in-vivo pharmacokinetic studies and long-term toxicity evaluations are recommended to establish clinical applicability and therapeutic safety.

Conclusion :

The present work demonstrates that curcumin-loaded niosomes are a promising nanocarrier system for enhancing the therapeutic potential of curcumin against breast cancer. The optimized formulation exhibited nanoscale particle size, high entrapment efficiency, good physical stability, and a sustained drug release profile. Physicochemical characterization confirmed successful drug encapsulation without any significant chemical interaction with excipients.

In-vitro cytotoxicity studies revealed superior anticancer activity of the niosomal formulation compared to free curcumin, which can be attributed to improved solubility, enhanced cellular uptake, and prolonged intracellular drug retention. These findings suggest that niosomal delivery can overcome the major biopharmaceutical limitations of curcumin, providing better tumor targeting and reduced systemic toxicity.

Overall, curcumin-loaded niosomes offer a safe, effective, and scalable drug delivery platform for breast cancer management. However, comprehensive in-vivo pharmacokinetic, biodistribution, and clinical studies are required to validate their therapeutic efficacy and establish their potential for translation into clinical practice.

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