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A Review Paper on Novel Lipid Nanoparticles for Enhanced Bioavailability of Bioactive Compounds in Breast Cancer Cell Lines

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Abstract

Most bioactive compounds from natural products are heavily relied on drug development due to their biological, chemical and pharmacological properties. Some compounds exhibiting anticancer properties have also been reported. However, they present a challenge in achieving the effective absorption and delivery in the body. This is due to minimal bioavailability, fluctuation of plasma drug concentration, low tolerance, first-pass effect which leads to less desired efficacy. Therefore, this calls for an innovative drug delivery means to overcome these medical challenges. Drug delivery strategies do utilize these elegant bioactive compounds because they are able to cross via systems barriers and deliver the compound to the cells or tissues. Lipid loaded nanoparticles, being a promising drug delivery system can protect therapeutics, such as hydrophobic, hydrophilic and amphiphilic compounds from unfavorable conditions such as pH and enzyme degradation and oxidation. The lipids in advance form influence the fate and the transport of drug in gastrointestinal tract through various mechanisms such as enhanced dissolution kinetics, triggers drug precipitation and enhance drug permeation when the lipid emulsion deplete. They also enhance pharmacokinetics such as increased stability, lengthening half-life, clearance and reduced side effects. They ensure sufficient solubility of drugs that have higher systemic toxicity, drug resistance possibility and poor targeting when used as free drugs thus improved bioavailability. This review aims to explore different lipid delivery systems of medicinal plant extracts, essential oils and bioactive compounds that deliver bioactive compounds from medicinal plants on breast cancer cell lines that aid in improving their bioavailability and thus improved efficacy.

Keywords: Therapeutic agents, target sites, solubility, bioavailability, solid lipid nanoparticles, drug delivery system

INTRODUCTION

Chemotherapies

Multidrug resistance (MDR) is one of the major challenges in breast cancer treatment drugs and these have led to cancer progression and chemotherapies failures [1]. Most chemotherapy is based on anthracyclines; Texans and doxorubicin being the major treatment option used. Chemotherapies is also used at pre-surgery to reduce the tumor mass and only about 40 % of patient achieve successful response [2]. This is due to the onset of drug resistance which is attributed to the presence of P-glycoprotein (Pgp) transporter which in many cases reduces efficacy of the adjuvant and neoadjuvant chemotherapies [2]. Additionally, chemotherapies have weak solubility, lack targeted delivery of drug to target cells, have inability to differentiate the normal cells and cancer cells, have short half-life. The chemotherapies success rate in treating breast cancer is still an unmet need.

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Medicinal Plant and Bioactive Compounds

Alternative treatment methods such as the use of medicinal plants; essential oils, extracts and herbs are being augmented being safer, easily biodegradable, easily available and having lower side effects compared to chemotherapies. Medicinal plants have been

considered by humans in treatment of breast cancer since the beginning of history [3].

Bioactive compounds are secondary metabolite isolated from medicinal plants and are responsible for anti-inflammatory, antioxidant and anticancer properties. Most of bioactive compounds have limitations which include low half-life, poor solubility, tolerability, stability, low cellular uptake/ internalization, low therapeutic index, and poor specificity [4, 5]. Most herbal medicine and convectional drugs are not able to rate and control the dosage to the target. Due to this, the drug is distributed to non-target cells, tissue and body fluid that could result into exceeding the amount required in target cells thus leading to adverse side effects. Nanotechnology as an interdisciplinary science, specifically lipid drug delivery system (LDD) is trying to overcome these challenges.

Lipid Drug Delivery Systems (LDDs)

The novel LDDs refer to spherical vesicles nanomaterial that are made of lipids and act as carriers. They have been developed as vehicles for bioactive compounds, thus maintaining drug concentration in therapeutic range and for a longer period and as per requirement. They contain ionizable cation lipids at low pH and neutral pH under physiologically conditions. They also contain nucleic acid cargo and other types of lipids. Due to their properties such as small size, lipid nanoparticles taken in via endocytosis and lipid ionizability at low pH allows endosomal escape. This allows the release of pharmaceutical ingredients into the cytoplasm. It also contains tristearin used as emulsifier. Additionally, LDDs contain polyethylene glycol (PEG) that minimizes opsonization, cholesterol that fills in the lipids gap and help in clearance of reticuloendothelial [6]. Also, the LDDs also help to minimize loss, drug degradation, facilitate accumulation of bioactive compound drug in site of action, instability, volatile, prevent drug toxicity, prolong drug plasma circulation half-life, improve low drug bioavailability, limited absorption, limited oxidative, degradation, prevent harmful side effects, poor aqueous solubility, lead to limited therapeutic efficacy and improve biological activity [7–9]. The examples of medicinal plants extract, essential oils and bioactive compound nanoparticles encapsulated with lipid delivery systems report in this review includes; curcumin-loaded solid lipid nanoparticles of *Aloe perryi* loaded nanosystems, solid-lipid nanoparticles containing essential oil of *Zataria multiflora*, docetaxel-loaded solid lipid nanoparticles, combination of Etoposide and quercetin-loaded solid lipid nanoparticles, *Pistacia atlantica* essential oil in solid lipid nanoparticles, encapsulated Oxovanadium(IV) and Dioxovanadium(V) complexes into solid Lipid nanoparticles, β-carotene loaded solid lipid nanoparticles, *Rosa damascena* essential oil loaded in nanostructured lipid carriers, syringic acid-loaded nanostructured lipid carriers, curcumin-loaded magnetic lipid nanoparticles, myricetin loaded into biocompatible lipid nanoparticles, solid-lipid nanoparticles containing *Mentha longifolia* and *Mentha pulegium* essential oils [8, 9] (Tables 1 and 2). Additionally, research has also been done on Silymarin and Silymarin loaded solid lipid nanoparticles, quercetin-loaded solid lipid nanoparticles and Hexahydrocurcumin-encapsulated chitosan nanoparticles [10, 11].

Method of Preparation of Lipid Nanoparticles

Cold Dilution of Microemulsion

This technique involves oil/ water O/W microemulsion (μE) that have dispersed oil phase containing solid lipid solution. This method is also a solvent diffusion technique. The water and solvent when saturated forms a stable micro emulsion. The cold dilution method involves the dilution of the initial micro emulsion using water at ambient or lower temperature. This then leads to a solid lipid formulation in a micro emulsion [12], as shown in Figure 1.

Probe Ultrasonic Melt-Emulsification Technique

This technique is composed of ultrasonic that contain sound waves that can modify, and probe samples being formulated. It is used in nanoemulsions and emulsions preparation. The ultrasonic physical effect is induced by acoustic cavitations of and it helps in disruption of oil droplets, thus leading to formation of O/W emulsion of nanosize. The important parameter that affects the efficiency of this technique is duration of emulsification, frequency and power of the ultrasonic waves. This technique is cheaper, energy saving and simple. The high-power low frequency ultrasound induces chemical/ biochemical, physical and mechanical changes via cavitation while low power high frequency

ultrasonic is used in monitoring physicochemical and composition of sample being formulated, as shown in Figure 2.

Table 1. Method of Lipid Nanoparticles Preparation Used.

Name of Lipid Nanoparticles	Method of Nanoparticle Preparation Used	Breast Cell Line Used
Curcumin-Loaded Solid Lipid Nanoparticles.	Cold dilution of microemulsion [12].	Human MCF-7 cells, human TNBC MDA-MB-231 and murine mammary cancer JC cells.
Herbal drug-encapsulated nanoniosome.	Thin film method [13].	MCF-7 and BT-474 cancer cells.
Aloe perryi loaded nanosystems.	Probe ultrasonic melt-emulsification technique [14].	(MCF-7) breast cancer cells.
Zataria multiflora essential oil solid lipid nanoparticles.	High pressure homogenizer method [15].	(MDA-MB-468) breast cancer.
Docetaxel-loaded solid lipid nanoparticles.	High-energy method [16].	Murine breast adenocarcinoma cells (4T1), human breast cancer cells (MCF7) and murine embryo fbroblast (NIH3T3) cells.
Combination of Etoposide and quercetin-loaded solid lipid nanoparticles.	Low-temperature emulsification and solidification methods [17].	MDA-MB-231 breast cancer.
Loading *Pistacia atlantica* essential oil in solid lipid nanoparticles.	Probe-ultrasonication method [18].	MDA-MB-231 cells.
Encapsulated Oxovanadium (IV) and Dioxovanadium(V) complexes into solid lipid nanoparticles.	Hot high-pressure homogenization [19].	MDA-MB-231 breast cancer cell line.
Rosa damascena Essential Oil Loaded in Nanostructured Lipid Carriers.	Probe ultrasonication method [20].	MDA-MB-231 human breast cancer cell line.
Syringic acid-loaded nanostructured lipid carriers.	Hot-melt emulsification method [21].	MCF-7 human breast carcinoma cells.
Curcumin-loaded magnetic lipid nanoparticles	Co-precipitation method [22].	MCF-7 breast cancer cell lines.
Docetaxel by myricetin loaded into biocompatible lipid nanoparticles.	Homogenization technique with ultrasonication size reduction [23].	MDA-MBA231 breast cancer cell.
Mentha longifolia and *Mentha pulegium* essential oils solid-lipid nanoparticles.	Pre-emulsion [24].	MDA-MB-468 and MCF-7.
Silymarin and Silymarin Loaded Solid Lipid Nanoparticles.	Hot homogenization method [25].	MCF-7 cells breast cancer.
Etoposide and quercetin-loaded solid lipid nanoparticles.	ultrasonic method and nanoemulsion [26].	MDA-MB-231 cells.
Hexahydrocurcumin-Encapsulated Chitosan Nanoparticles.	oil-in-water emulsification and ionotropic gelation and optimized using the Box–Behnken design [27].	MDA-MB-231 Breast Cancer Cells.

High Pressure Homogenizer Method

This technique uses high pressure gradient turbulence, and this produces shearing forces because of depressurization of suspension that is highly compressed at pressure of 900 bar. The pressure usually pumps the liquid via a narrow gap that is formed by the stationary parts. The velocity can reach up to 200m/s causing the hydraulic shear. The size of the gap in the homogenization valve regulates the values of the forces used. This technique has been employed in mixing, stabilization and comminution of nanoparticles [28]. The method has been used in preparation of non-vesicular and vesicular lipid based nanosystem, nanocrystals, polymeric nanoparticles and nanostructured lipid carrier [29], as shown in Figure 3.

Table 2. Advantages and Disadvantages of Lipid Nanoparticle Preparation Methods.

Methods	Advantages	Disadvantages

Cold dilution of microemulsion.	It is a convenient and efficient way of preparing lipid nanoparticles especially in small scale application.	Requires a large amount of co-surfactants and surfactants to stabilize the lipid nanoparticles since its easily influenced by environmental factors such as pH and temperature.
Soxhlet method.	This method can help to maintain the stability of the nano-formulated drug, thus enhancing its controlled drug release.	The plant compound to be formulated must be soluble in solvent at high temperature.
Probe ultrasonic melt-emulsification technique.	The method is easy, straight forward and does not require toxic organic solvents.	This technique requires customization for each specific drug, thus consistence results achievement of different compounds drugs is a challenge.
High pressure homogenizer method.	This is the most scalable and versatile technique for different non-vesicular and vesicular lipid based nanosystems, e.g., solid lipid nanoparticles, polymerics and nanocrystals, nanostructured lipid carriers nanoparticles.	This technique can induce degradation of during drug formulation and can also cause uncertain drug transitions such as gelation and crystallization.
High-energy method.	This technique enhances uptake and retention of lipid nanoparticles since the method exhibits biodegradation, biocompatibility and small size nanoparticles.	This method requires some specialized and expensive mechanical device which can be expensive to maintain and consume large amount of energy that cannot be sustained for large scale nanoparticle production.
Low-temperature emulsification and solidification methods.	Enhance drug stability, thus helping to maintain the integrity of lipid matrix. This helps to reduce drug degradation during the formulation.	This technique can struggle to precisely process the dispersion of nanoformulated compound in the emulsion.
Co-precipitation method/ Solvent displacement method/ interfacial deposition method.	Uses biodegradable polyesters such as poly (lactide-co-glycolide) (PLGA), poly(***ϵ***-caprolactone) (PCL), and poly(lactide)(PLA).	Achieving size control, distribution control and the morphology of nanoformulated drug is still a challenge.
Pre-emulsion method.	This method ensures efficient encapsulation of the hydrophobic drug within the core of drug delivery system.	Controlling size distribution can be difficult, achieving emulsion stability of lipid nanoparticles can also be a challenge due to coalescence and phase separation.
Ionotropic gelation method.	This is an easier and affordable technique.	The technique can result in uneven coating of the lipid nanoparticle and the release of encapsulated drug may not be consistent.

High-Energy Method

This technique involves use of high energy in preparation of nanoemulsion of uniform droplets size below 100nm. They include sonication, high shears stirring method, micro fluidization, jet dispenser, high pressure homogenization. The droplet size of nanoemulsion depends on production conditions such as temperature, time, equipment, composition and property of sample. High energy method usually consumes a lot of energy and requires sophisticated equipment, thus is very expensive. Their advantage is that they require control of droplet size and large integral component selection [30].

Low-temperature Emulsification

This technique is used to prepare solid lipid micro and nanoparticles. This method helps to minimize energy during formation of a drug delivery system. This temperature helps to change the non-ionic surfactant curvature called phase inversion temperature. The low energy control droplets size. The low energy method includes phase inversion method, solvent displacement method and spontaneous emulsification [31].

Solvent Displacement Method

This technique is also called co-precipitation method/ nanoprecipitation method or interfacial deposition method. This technique involves trapping of the active molecules at nanosize or submicron. A sample is placed in a column, then displaced with a solute. The method involves rapid solvent

diffusion in external aqueous phase. The method is fast, reproducible and convenient. The method is used to prepare polymeric and monodisperse nanoparticles [32], as shown in Figure 4.

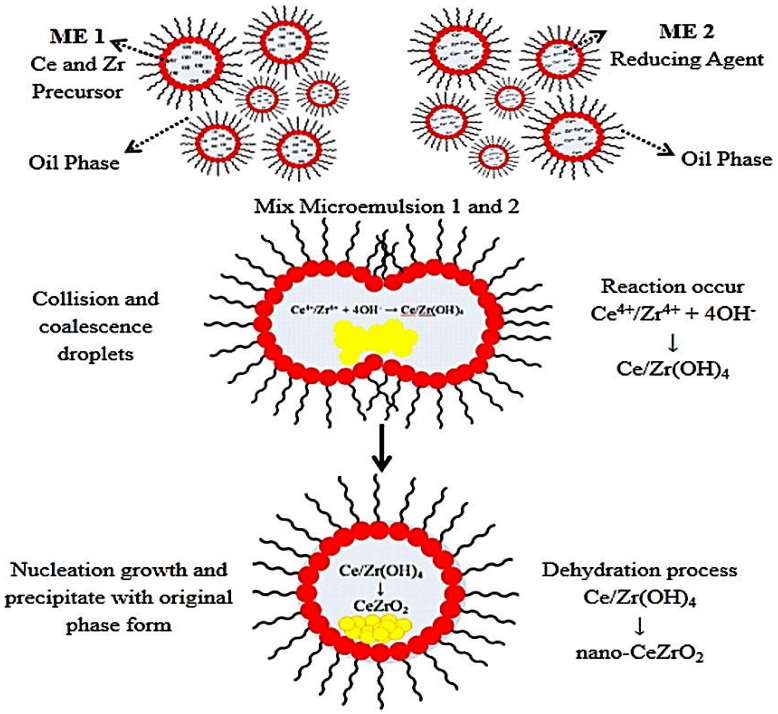

Figure 1. This figure shows how nanoparticles are formed using cold dilution method.

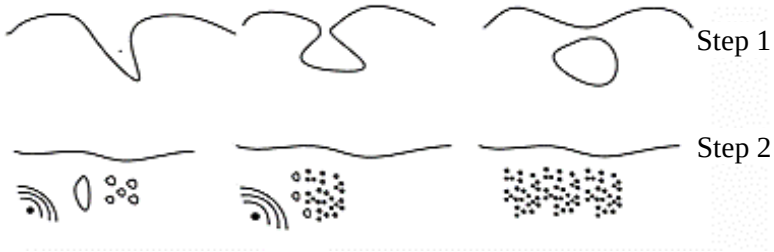

Figure 2. Emulsification using ultrasonic technique.

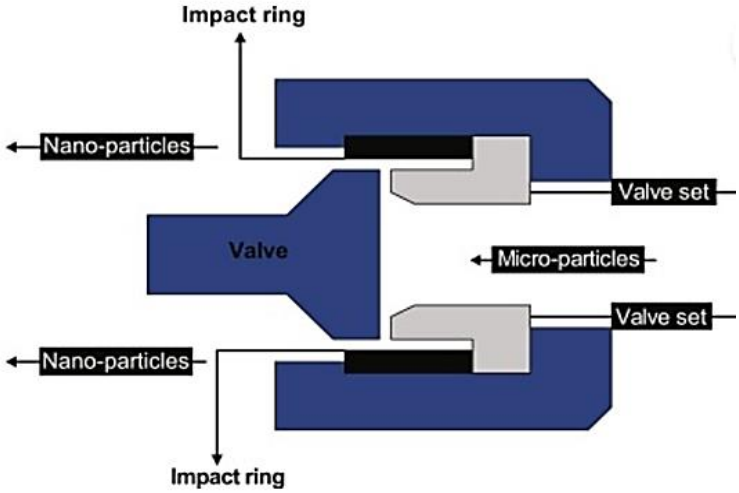

Figure 3. This figure shows homogenization technique for nanoparticle preparation.

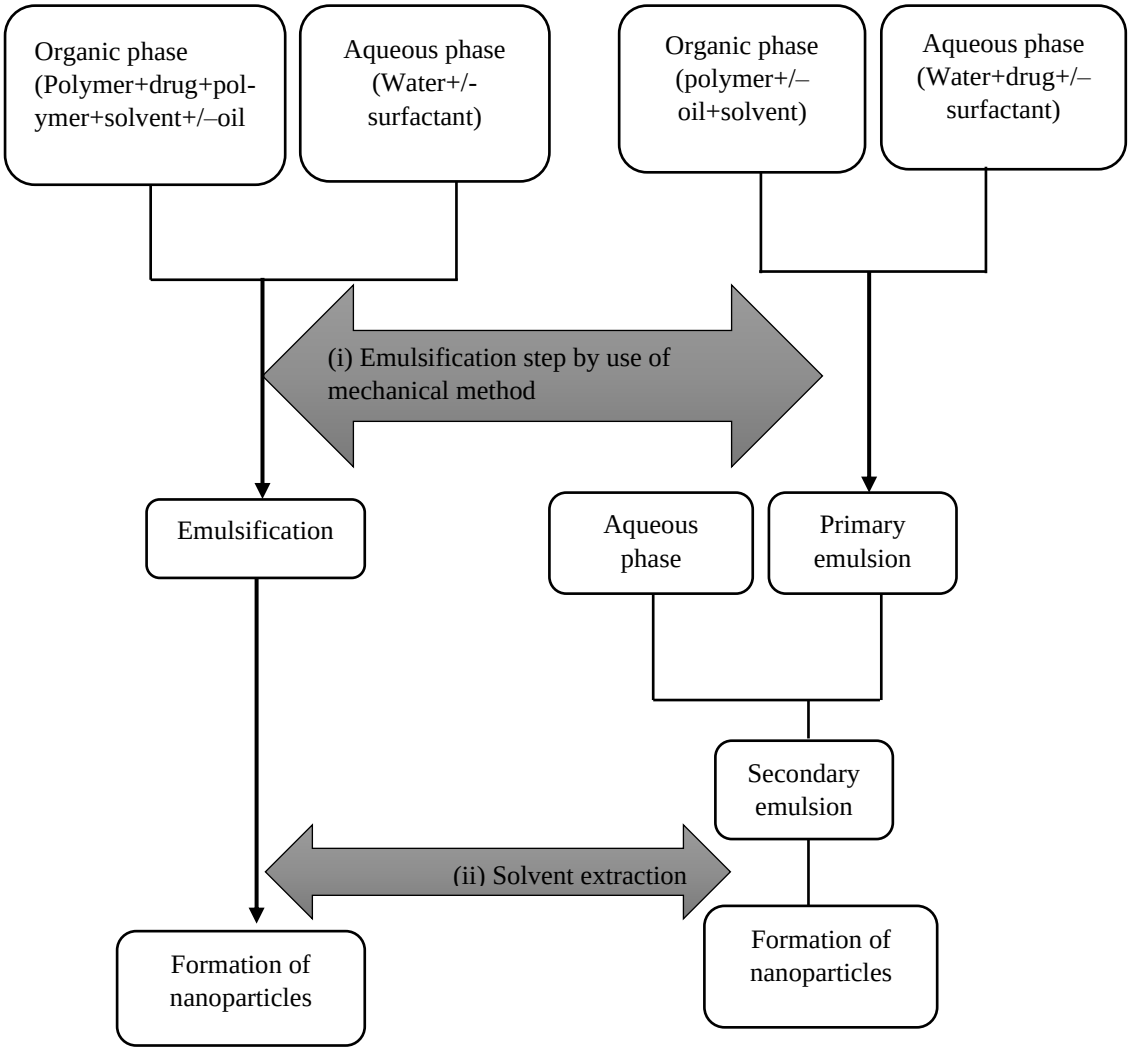

Figure 4. The schematic diagram above represents nanoparticles formation using solvent displacement method.

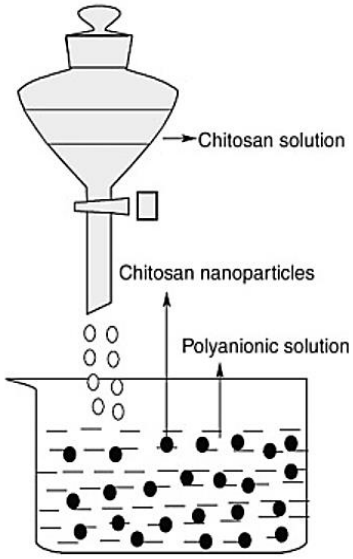

Figure 5. The ionotropic gelation technique that leads to formation of nanoparticle.

Pre-Emulsion Method

This is a technique that is used in preparation of emulsions. It is a method that is used in emulsion stabilization via intense stirring which increases oil binding capacity. The oil droplet that has been treated is subjected to a polymer and the techniques enhances their interaction. Water and surfactant are major components of this method [33].

Ionotropic Gelation Method

This method uses polyelectrolyte which crosslinks in the presence of phosphate group such as sodium tripolyphosphate (STT). The polysaccharide and positively charged chitosan are dissolved in acidic solvent which is added drop wise while stirring leading to formation of polyanionic solution. This method is used in encapsulation of protein [34], as shown in Figure 5.

CONCLUSION

Lipid delivery systems' nanoparticles are novel delivery systems that have better characteristics than the convectional drug. They are more bioavailable thus enhance the solubility of drugs. The importance of these drugs delivery systems includes optimum dosage at right target, improved therapy, enhanced solubility and the biopharmaceutical drug performance and thus improved standard of living.

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Author Contributions

Conceptualization, JN.; Writing – Original Draft Preparation JN, Writing – Review & Editing JN.

Conflicts of Interest

The author declared no conflict of interest.

Data Availability

Data supporting the results of this study shall, upon appropriate request, be available from the corresponding author.

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