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Current trends in Nano-vesicle niosomes for delivery of bioactives and their potential applications

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Abstract
Rapid progress in development and application of nanotechnology has been extensively studied and well documented in the fields of pharmaceuticals, foods and cosmetics from the past few decades. The problems associated with bioactives are poor bioavailability, low aqueous solubility and membrane permeability. Niosomes are novel Nano-vesicles which exhibits chemically stable, biodegradable, biocompatible and non-immunogenic, longer shelf life, targeted delivery in controlled and sustained release manner of bioactives. This review mainly focussed on structure, formulation aspects of niosomes, methods of preparation, advantages and applications of bioactive loaded niosomes into foods.

Keywords: Niosomes, bioavailability, fortification, bioactives, nanovesicles

Introduction
Vesicular systems are bilayer vesicles and have received a great attention of delivering the bioactive substances in more controlled manner, improve bioavailability and gives the therapeutic effect for a prolonged period of time. They consists amphiphilic molecules that surrounded by aqueous compartment, which helps encapsulating both hydrophilic and hydrophobic compounds. The lipid based vesicles liposomes and niosomes was successful methods to deliver the active substances, therefore attracted the researchers, as they possess many advantages over conventional methods. Liposomes are the first vesicular bioactive delivery system but have several drawbacks such as phospholipids are expensive and availability with high purity is difficult which influences the size and shape of vesicles, low chemical stability, sterilization, toxicity, presence of ester bond in phospholipids are easily oxidized or hydrolysed, large scale production and physico chemical stability like aggregation, fusion or sedimentation of liposomes during storage, low shelf life (Ahmad *et al*., 2016) [1]. Therefore the research interest is shifted to the novel niosomal nanoparticles with a range in between 0.1 to 100 nm to overcome these problems. Reducing the vesicle size to nanoscale offers protecting the bioactives from degradation in gastrointestinal circulation, sustained release manner and targeted delivery of therapeutic components to specific site. It also solves the challenges associated with bioavailability, stability and toxicity (Seleci *et al*., 2016) [32].
Niosomes are bilayer vesicles which are formed by self-association of non-ionic surfactants (e.g: alkyl ester or alkyl ether) in addition to, stabilizers in many cases cholesterol. Since the name "*Nios"* means non-ionic surfactant and "*somes"* means vesicles therefore named as niosomes and they are non-toxic because of surfactants. They can be utilized for both lipophilic and hydrophilic bioactives, which entraps in to vesicular membrane and aqueous core respectively. Due to their unique structure they are promising tools in the nanotechnology industry (Moghassemi and Hadjizadeh, 2014) [22]. The vesicles do not form spontaneously, thermodynamical stable vesicles are formed in the presence of proper amount of non-ionic surfactants and membrane stabilizers at a temperature above the gel-liquid phase transition of main lipid. The thin lipid film of non-ionic surfactant is hydrated in aqueous media and imbibing the bioactive containing hydrating solution. Agitation makes the detachment of lipid sheets and then self-associate to form stable niosomes (Pardakhty and Moazeni, 2013) [26]. Niosomes are chemically stable, biodegradable, biocompatible and non-immunogenic. They exhibits longer shelf life, targeted delivery in controlled and sustained release manner, protects from harsh biological gastro intestinal environment, more penetrability and delays the clearance (Sankhyan and Pawar, 2012) [31]. This review includes the latest information on niosomes including structure, formulation aspects, factors affecting the properties of niosomes, methods of preparation, characterization, advantages and food applications with bioactive loaded niosomes.

Structure of niosomes

Niosomes are bilayer vesicles formed by non ionic surfactants agents with or without stabilizers and charge inducers. Thermodynamic stable niosomes are only prepared with admixture of proper amount of surfactant and stabilizers. Different types of non ionic surfactants at variable molar ratios and combinations are used to form stable niosomes. Addition of stabilizers mainly cholesterol is used to maintain the rigidity of bilayer which results in to less leaky niosomes. Addition of charge inducers provide the surface charge and help to stabilize the bilayer vesicles. The vesicles are spherical in shape and consist of unilamellar or multilamellar structures. Because of its versatile structure and special geometry, niosomes helps to entrap both hydrophilic and hydrophobic compounds partitioning the molecules into bilayer system. The non ionic surfactants tends them to orient the hydrophilic end align towards the aqueous compartment (outward) and hydrophobic end faces inward phase to form a closed bilayer structure as shown in Fig 1. Hence the closed bilayer structure of niosomes has inner and outer surfaces of hydrophilic sandwiched with lipophilic domain in between (Gandhi *et al*., 2012; Bhardwaja *et al*., 2020) [6, 3]. To form thermodynamical stable bilayer structure, sufficient energy from external source must be required into the system such as heat, shaking, pressure, ultrasound and physical agitation etc. Various forces such as vander wall or repulsive forces that exist between the surfactant molecules play an important role to maintain the vesicular bilayer structure. These forces are derived from the hydrophilic head group which remain contact with water; and the hydrophobic interactions between hydrocarbon tails causes the molecules to associate. Therefore the two interactions compete with each other and gives rise to two opposite forces which act mainly in interfacial region, one tend to increase and other tend to decrease when exposed to aqueous phase.

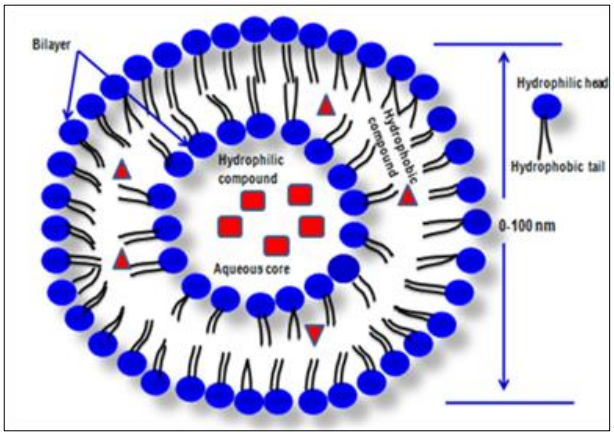

Fig 1: Structure of Niosomes

Formulation: structural components of niosomes

The basic components that are used for preparation of niosomes are non ionic surfactants, stabilizers, charge inducers and hydration medium. It is important to understand the use of components in formulation and their effects on physico–chemical characterization and stability of niosomes.

Non ionic surfactant

Non ionic surfactant (NIS) belongs to class of surfactant, which have no surface charge in their hydrophilic head. It is a principal component used for preparation of niosomes. They comprise of polar and non polar moieties which possess high interfacial activity, upon hydration it forms bilayer and hence, can entrap both hydrophilic and hydrophobic compounds. The hydrophobic group may consist of 1 or 2 or 3 alkyl chains or single stearyl or perfluoro alkyl group. Hydrophilic head moiety may affect the entrapment efficiency of bioactive, due to more interfacial tension between aqueous phase and the hydrophobic alkyl chain, which leads to aggregation of monomers units (Swarnali and Dharampal, 2017) [35]. They can form a unique structure in solutions where, the hydrophilic heads are opposite to aqueous solutions and hydrophilic tails are opposite to organic solvents. Therefore, niosomes are formed by self assembly of NIS because to this property in aqueous media. They are preferred mainly due to their properties such as high stability, non toxic, biocompatible, maintain the physiological pH compared to anionic, cationic or amphoteric (zwitterionic) surfactants. They increase the bioavailability of many bioactives including some anticancer and HIV drugs by inhibiting the p-glycoprotein (Moghassemi and Hadjizadeh, 2014; Mahale *et al*., 2012) [22, 18]. They have ability to enhance aqueous solubility of poor water soluble active substances and hence improve the bioavailability, they can acts as stabilizers, emulsifiers, wetting agents and permeability enhancers. A wide range of NIS with different combinations and molar ratios has been studied to entrap the bioactive substances of varying vesicle size (Sankhyan and Pawar, 2012) [31].

Stabilizer

Stabilizer is an important additive for niosome preparation; most widely used membrane stabilizer is the cholesterol. Cholesterol is an amphiphilic compound which does not produce vesicles and generally used along with non ionic surfactant to obtain bilayer structure. It acts as a “mortar” by virtue of its shape as well as solubility properties, it fills the empty spaces thereby bind them more strongly with surfactants into the bilayer. Thus restricts the movement of hydrocarbons of surfactants that results into decrease in permeability of cholesterol. It interacts with surfactant across hydrogen bonding between hydrocarbon chain of surfactant and hydroxyl group of cholesterol, consequently enhances the membrane cohesion and mechanical stiffness (Swarnali and Dharampal, 2017) [35]. It affects the properties of niosomes including stability, provides rigidity, improves the rate of entrapment capacity, release rate, storage time, prevents or decreases the leakage from membrane by changing the transition state from gel to liquid phase (Tc) and toxicity. Amount of addition of cholesterol depends upon the HLB value of surfactant. The surfactants whose HLB value is >6, need to add cholesterol to form niosomes, whereas if HLB value <6, it enhances the stability of bilayer vesicles (Moghassemi and Hadjizadeh, 2014) [22]. As HLB value is above 10, it is necessary to add the higher amount of cholesterol to compensate the large head group. Generally cholesterol is added in 1:1 ratio with surfactant (Kumar and Rajeshwarrao, 2011; Bhardwaja *et al*., 2020) [15, 3].

Charge inducers

Charge inducers are another prevalent component used in niosome preparation, to confer electrostatic stability by increasing the surface charge thereby it prevents the vesicle fusion, flocculation and aggregation (Keshav, 2015) [13]. It prevents the fusion of vesicles which could be due to the

repulsive forces and imparts higher zeta potential. Dicetyl phosphate, phosphatidic acid, dihexadecyl phosphate are most commonly used negatively charged inducers and stearylamine and stearyl or cetyl pyridinium chloride are used as positively charged molecules in preparation of niosomes. The optimum concentration of addition is about 2.5-5 mol %, increasing the amount beyond the level may inhibit the formation of niosomes (Gharbhavi *et al*., 2018) [7].

Hydration medium

Phosphate buffer at diverse pH is most normally used as hydration medium for niosome preparation. pH of hydration medium is an important factor that affects the entrapment efficiency. Selection of actual pH of hydration medium will depends upon the solubility of bioactive compound being encapsulated. For hydrophilic compounds the optimum pH should be buffered around 7; whereas for hydrophobic compounds, slightly acidic pH about 5-6 should be used as hydration medium (Kumar and Rajeshwarrao, 2011; Mahale *et al*., 2012) [15, 18].

Methods of Preparation of Niosomes

Thin-Film Hydration Method

Thin-film hydration method is a simple and widely used method for preparation of niosomes. In this method, the non-ionic surfactants, stabilizers and charged molecules if desired are dissolved in an organic solvent such as alcohol, in a round bottomed flask. Then, the organic solvent is removed using a rotary vacuum evaporator to form a thin film on the inside wall of the flask. An aqueous solution of drug is added and the dry film is hydrated above the transition temperature of the surfactant for specified time with constant shaking (Bhaskaran and Lakshmi, 2009) [4]. Multilamellar niosomes are formed by this method. This method is widely used to formulate niosomes loaded with drugs such as insulin, doxorubicin and other extracts (Tavano *et al.*, 2013) [37].

Ether Injection Method

In ether injection method, the surfactants with additives such as charged molecules are dissolved in diethyl ether and injected slowly through a needle in an aqueous drug solution maintained at a constant temperature, which is above the boiling point of the organic solvent. The organic solvent is evaporated using a rotary evaporator. During the vaporization, the formation of single layered vesicles occurs (Marwa *et al.*, 2013) [21]. Niosome formulation of stavudine prepared by ether injection technique showed great potential in the treatment of HIV by providing a prolonged release profile (Shreedevi *et al.*, 2016) [32]. Sailaja and Shreya, (2018) [30] prepared and characterized naproxen loaded niosomes by ether injection method.

Reverse Phase Evaporation Method

In this method, surfactants, stabilizers and additives are dissolved in a mixture of ether and chloroform and added to aqueous phase containing the bioactive component. The obtained mixture is sonicated in order to get an emulsion and finally, the organic phase is evaporated. Large unilamellar vesicles are formed during the evaporation of the organic solvent. BSA-Basic fibroblast growth factor loaded niosomal nanovesicles were successfully prepared by reverse-phase evaporation technique with 57.885 ± 0.387% of EE% and an average particle size of 232 nm (Moghassemi *et al.*, 2017) [23]. Insulin loaded niosomes coated by TMC was successfully formed by reversed-phase evaporation technique.

Microfluidization Method

The microfluidization method is based on the principle of submerged jet. In this method, the bioactive compound and the surfactant fluidized streams interact at ultrahigh velocities, in precisely defined micro channels within the interaction chamber. The high speed impingement and the energy involved results in the formation of niosomes. Obeid *et al.* (2017) [25] successfully prepared non-ionic surfactant vesicles for delivering therapeutic siRNA into cancer cells using microfludics device Nanoassemble. Niosomes size was found below 60 nm, with relatively low polydispersity index and good stability for over 8 weeks at 25ºC.

Supercritical Carbon Dioxide Fluid (scCO2)

Manosroi *et al.* (2010) [20] have described the supercritical reverse phase evaporation technique for niosome formation. They added Tween 61, cholesterol, PBS, glucose and ethanol into the view cell and then CO_2 gas was incorporated into the view cell. Magnetic stirring was done till equilibrium was attained, after that pressure was released and niosomal dispersions were formed. This method enables one step production and easy scale-up.

Proniosomes

Proniosome technique employs the coating of a water-soluble carrier like mannitol and sorbitol with non-ionic surfactant. The coating process leads to the formation of a dry formulation. This preparation is known as "Proniosomes", and the addition of the aqueous phase results in the formation of niosomes. This method helps in reducing physical stability problems such as the leaking, aggregation and fusion and also provides convenience in dosing, transportation, distribution and storage showing better results compared to conventional niosomes (Swarnali and Dharampal, 2017) [35].

Transmembrane pH Gradient

In this method, non ionic surfactant and stabilizer are dissolved in chloroform and evaporated to form a thin lipid film on the inside wall of a round bottomed flask. The thin film formed is hydrated with a solution of citric acid by vortex mixing and the product formed is freeze-thawed for niosome preparation. The aqueous solution of bioactive is added to this niosomal suspension and pH between 7.0 and 7.2 is maintained with the addition of phosphate buffer. According to this method, the interior of niosome has a more acidic pH compared to outer medium. The added unionized bioactive compound passes through the niosome membrane and enters into the niosome. The bioactive compound ionizes in an acidic medium and thus, cannot escape from the niosomal bilayer (Verma *et al*., 2010) [38].

Heating Method

This is a patented method, which was developed by Mozafari (2005) [24]. Surfactants and stabilizer are separately hydrated in buffer and the solution is heated to 120°C with stirring to dissolve stabilizer such as cholesterol. The temperature is decreased and surfactants and other additives are then added to the buffer in which cholesterol is dissolved with continuous stirring. After this, niosomes formed are kept at room temperature, and then stored at 4-5°C under nitrogen

atmosphere till further use (Moghassemi and Hadjizadeh, 2014) [22]. α-Tocopherol loaded niosomes were prepared using modified heating method (Basiri *et al.*, 2017) [2].

Bubble Method

This method employs addition of surfactants, additives and the buffer into a glass flask with three necks. Niosome excipiebnts are dispersed at 70 °C and the resulted dispersion is mixed with homogenizer. Immediately the flask is placed in a water bath after mixing followed by the bubbling of nitrogen gas at 70 °C. Nitrogen gas is passed through a sample of homogenized surfactants resulting in formation of large unilamellar vesicles (Talsma *et al.*, 1994) [36].

High-Pressure Homogenization

High pressure milling is the main force, which results in the formation nanosized particles in this technique. Preformed polymers and bioactives are dispersed in medium, and subjected to high pressure homogenizer. Usually the pressure is increased step by step, in order to eliminate clogging of the particles in the narrow homogenizer hole (Kipp, 2004) [14]. The common types of equipment used to produce nanoparticles in high-pressure homogenization method are the microfluidizer and the piston-gap homogenizer. The final size of nanoparticles will depend on the applied pressure, and the number of homogenization rounds. Niosome nanodispersion loaded with beclometasone dipropionate (BDP) was prepared using high-pressure homogenization following the hydration of proniosomes (Kaialy and Al Shafiee, 2016) [11].

Advantages of niosomes

Niosomes is preferred due to several advantages when compared with liposomes and other conventional methods.

- Niosomes are chemically more stable and osmotically active, have long shelf life when compared with liposomes.
- The surfactants in niosomes are biocompatible, easily biodegradable, non-immunogenic and non-toxic due to non-ionic nature.
- Due to the versatile and unique structure, they can entrap a wide range of bioactives of hydrophilic, lipophilic and amphiphilic compounds.
- The shape, size, surface and entrapment can be formed or modified easily due to the presence of functional group on hydrophilic head or using different additives in combination and ratios.
- They are capable of delivery the bioactive in controlled and sustained manner at targeted site and delay clearance from biological circulation.
- Enhances the absorption, bioavailability, permeability and efficacy of poorly soluble bioactive compound.
- They are cost effective and do not require any special conditions like inert atmosphere or low temperature for handling and storage of surfactants.
- Preparation of niosomes is very easy, the raw materials are relatively affordable, easily available and no sophisticated equipments are required.
- Better patient compliance since the vesicle suspension is in water based vehicle system than compared to oil based forms.
- Exhibit flexibility in control of vesicle characterization by altering type of method of preparation, composition, size, entrapment efficiency, fluidity, lamellarity, surface charge, concentration and volume of various additives.
- Protects and enhance the therapeutic properties of bioactive substances from harsh gastrointestinal conditions and enzymatic degradation.
- Niosomes can be administered across all routes by oral, transdermal, parenteral, pulmonary and ocular (Bhardwaja *et al*., 2020; Keshav, 2015; Moghassemi and Hadjizadeh, 2014) [3, 13, 22].

Applications of Niosomes

Niosomes are novel nano drug carriers to design effective delivery systems. Niosomes were first used in cosmetic industry and after that gained attention of the pharmaceutical companies. They have enormous potential for therapeutic applications of the bioactive components being the subject of an intensive research studies. They offer a great opportunity for incorporating hydrophilic, lipophilic bioactives or both bioactive components together. Many recent investigations have utilized niosomes for enriching various food products and for pharmaceutical purposes. *Ginkgo biloba* extract (GbE) was studied for human brain and breast cancer prevention; GbE loaded niosomes (Tween 80, Span 80, and Cholesterol) after oral administration showed an increase of *in vivo* distribution when compared to GbE tablet (Jin *et al.*, 2013) [9]. Niosome formulations loading *Gymnemasylvestre* extract showed significant blood glucose level reduction and increased antihyperglycemic activity compared with the parent extract (Kamble *et al.*, 2013) [12]. The increasing number of studies on natural products can lead to consider niosomes as promising carriers, by different routes of administration, in pharmaceutics, in cosmetics as well as for food applications. Moghasemmi *et al.* (2017) [23] prepared niosomes loaded with BSA and reported that these niosomes were able to slowly release BSA molecules in PBS and release profile of molecules can be controlled by the cholesterol percentage as one of the formulation parameters. In other study, Moghasemmi *et al.* (2017) [23] stated that combination of nano-niosomes as a drug delivery system with a simple agarose hydrogel as a scaffold could be successfully used for preserving growth factor's biological activity and to provide a sustained release profile. While successful application of niosomes was adopted for several bioactivities. Depending on the type of bioactive and their delivery requirements, niosomes are utilized for various applications, which are listed in Table 1.

Table 1: Application of niosomal formulation loaded with bioactive components

Bioactive compound	Components	Preparation method	Application	References
Catechin entrapped niosomes	Tween 60 and lauryl alcohol	Thin film hydration with high shear homogenization	Improved bioavailability of catechins and exhibited higher antioxidant activity in milk	Gadapa *et al.* (2022) [5].
Casein biopeptide loaded niosomes	Tween 60 and lauryl alcohol	High shear homogenization	Exhibited lower particle size with enhanced bioavailability and sustain	Sonia Mor *et al.*, (2021) [3].

			release.	
Isoleucine-Proline-Proline	Tween (20, 40, 80), span (80) and cholesterol	Thin film hydration with sonication	Sustained release behaviour in simulated blood fluid	Rezvani *et al.* (2019) [29].
Resveratrol loaded niosomes	Span 60 and Tween60, cetyl alcohol or stearic acid	Thin film hydration followed by sonication	Controlled release under simulated gastro intestinal conditions and high intracellular ROS scavenging activity	Sravani *et al.* (2018) [35].
Canthaxanthin entrapped niosomes	Tween (60, 80), Span (60, 80) and cholesterol	Thin film hydration	Higher stability	Ravaghi *et al.* (2017) [28].
Iron entrapped niosomes	Span 80 and lauryl alcohol	Ethanol injection	Did not effect the textural and rheological properties.	Gutierrez *et al.* (2016)
EGCG loaded niosomes	Tween 60 and cholesterol	Ethanol injection	Improved chemical stability and antioxidant property	Liang *et al.* (2016) [17].
Resveratrol entrapped niosomes	Gelot 64 and unsaturated fatty acids (oleic and linoleic acids	Thin film hydration followed by sonication and ethanol injection	Higher entrapment efficiency and good stability	Pando *et al.* (2015) [8].
Ferrous sulfate and vitamin D_3	Span 60 and cholesterol	Supercritical carbon dioxide fluid	Higher entrapment efficiency and stability	Wagner and Rizvi (2015) [40].
Ellagic acid loaded niosomes	Span 60 and Tween 60, cholesterol	Thin film hydration followed by extrusion process	More stable with highest entrapment efficiency	Junyaprasert *et al.* (2012) [10].
Catechin and EGCG	Span 60 and cholesterol	Thin film hydration	Controlled and sustained release of catechins	Li *et al.* (2012)
Rice bran niosomes	Tween 61, stearic acid and cetyl alcohol	Supercritical carbon dioxide fluid	Increased antioxidant activity	Manosroi *et al.* (2012) [19].
Rh-Insulin	Polyoxyethylene alkyl ether, cholesterol, dicetylphosphate	Modified handshaking method	Protection against proteolysis, sustained release	Pardakhty *et al.* (2011) [27].

Conclusion

Niosomes are novel nano technology approach which reduces the size of bioactive compound in between 0.1 to 100 nm to overcome various problems. Reducing the vesicle size to nanoscale offers protecting the bioactives from degradation in gastrointestinal circulation, sustained release manner and targeted delivery of therapeutic components to specific site. It also solves the challenges associated with bioavailability, stability and toxicity.

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Author's contribution: GS and BSN: Acquisition of data and substantial contribution to the conception and design; drafting or critically revising the manuscript.

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