International Journal of Applied Pharmaceutics

ISSN- 0975-7058 Vol 12, Issue 6, 2020

Review Article

# SOMES: A REVIEW ON COMPOSITION, FORMULATION METHODS AND EVALUATIONS OF DIFFERENT TYPES OF "SOMES" DRUG DELIVERY SYSTEM

**KUSUMA PRIYA M. D.[a], VINOD KUMAR[a], DAMINI V. K.[a], ESWAR K.[a], KADIRI RAJESH REDDY[b], BRITO RAJ S.[a*], SUCHARITHA P.[c]**

**[a]Department of Pharmaceutics, Centre for Pharmaceutical Nanotechnology, Sri Venkateswara College of Pharmacy, RVS Nagar, Chittoor 517127, Andhra Pradesh, India, [b]Department of Pharmaceutics, Mahathi College of Pharmacy, Madanapalle 517319, Andhra Pradesh, India, [c]Department of Pharmaceutics, Seven Hills College of Pharmacy, Tirupati 517561, Andhra Pradesh, India**
**Email: britosraj@yahoo.co.in**

*Received: 10 Jul 2020, Revised and Accepted: 24 Aug 2020*

**ABSTRACT**

Many drugs are available in the market for several diseases, disorder or even for a condition, but it is difficult to select a suitable carrier to attain maximum bioavailability and potential for a potent drug. Attaining a controlled and sustained release of a drug is purely focused on the selection of a carrier (natural, synthetic and hybrid) like nanosomes. Nanosomes have become a prominent tool in the field of pharmacy. Nanosomes are small uniform structures which deliver the drug to the specific targeted site, which mainly depends upon the presence of ligands, shape, size and surface chemistry. Nanosomes are available in various types which include Niosomes, Liposomes, Electrosomes, Aquasomes, Transfersomes, Phytosomes, Enzymosomes, Ethosomes, Invasome and Sphingosomes. In general, all these nanosomes are quite similar in nature with minute differences in their vesicular characteristics and composition. This review traces various 'Somes' composition and their role in the formulation, applications, advantages, disadvantages, common formulation procedures and evaluation parameters.

**Keywords:** Nanosomes, Drug targeting, Formulation, Surfactants and phospholipids


DOI: http://dx.doi.org/10.22159/ijap.2020v12i6.38996. Journal homepage: https://innovareacademics.in/journals/index.php/ijap

## INTRODUCTION

Though different drugs are available in the market for a spectrum of disease, disorder or even for a condition, their drug delivery system plays a key role in it, starting from avoiding unnecessary side effect still their cost effectiveness. Formulating a rational formulation is a challenging process for a pharmacist. In which, it is difficult to select a suitable carrier to attain maximum bioavailability and potential for a potent drug.

In 1909, Paul enrich developed and initiated the Drug targeting era. In drug targeting the active medicament or the therapeutic agent of a drug reaches the targeted site without getting metabolized through escaping from the first pass metabolism, with improved bioavailability and reduced unintended side effects.

Attaining a controlled and sustained release of a drug is purely focused on the selection of a carrier like nanosomes for a drug represented in fig. 1. Nanosomes are small uniform structures which delivers the drug to the specific targeted site, which mainly depends upon the presence of ligands, shape, size and surface chemistry. Based on different aspects like therapeutic uses, lipoidal and nonlipoidal barriers they are of different types which includes Niosomes, Liposomes, Electrosomes, Aquasomes, Transfersomes, Phytosomes, Enzymosomes, Ethosomes, Invasome and Sphingosomes [1-10].

The drugs can be encapsulated into the different types of vesicular structures using various types of mechanisms and formulation methods. The various 'Somes' composition and their role in the formulation, applications, advantages, disadvantages, common formulation procedures and evaluation parameters were discussed below.

Articles are reviewed from 1975 to 2020 and keywords used for this review are the preparation, evaluation, and application of niosomes, liposomes, electrosomes, aquasomes, transfersomes, phytosomes, enzymosomes, ethosomes, invasomes, sphingosomes.

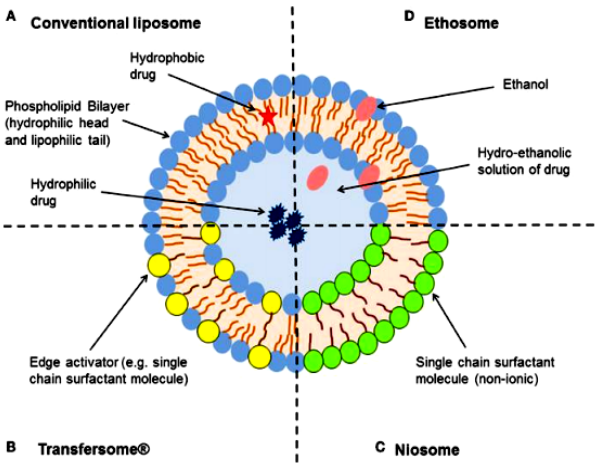


**Fig. 1: Structures of various somes [21, 28, 51, 72, 74]**

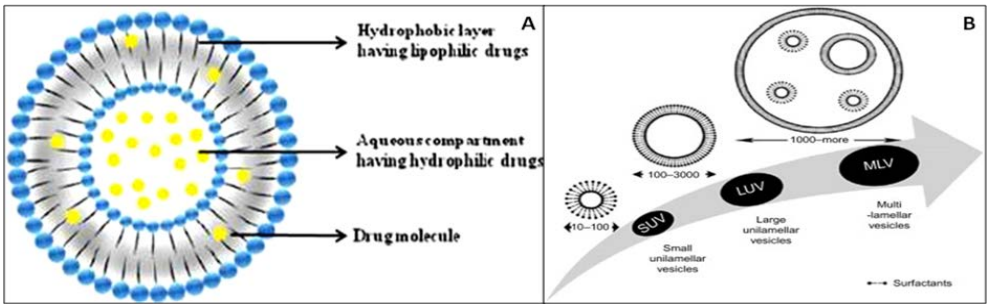


**Fig. 2: (A) Structure of Noisome; (B) Types of niosomes**

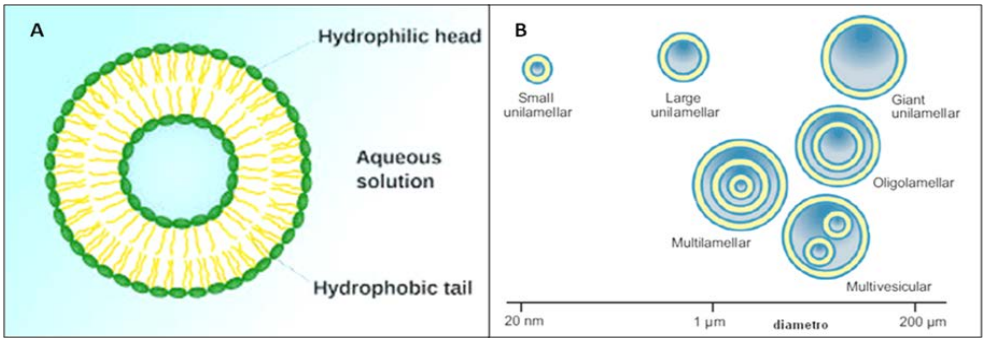


**Fig. 3: (A) Structure of liposome; (B) Liposomes types based on size [21, 28, 38, 39, 51]**

**Niosomes**

The main perspective of developing niosomes to overcome the problems related to sterilization, large scale production and stability. Niosomes are thermodynamically vesicles, which are similar to liposomes and microscopic in size ranges on a nanometric scale ideally suitable for transdermal delivery. It is composed of hydrated compounds of cholesterol, charge inducing substances and nonionic surfactants like mono alkyl and dialkyl polyoxy ethylene ether used mainly carriers of lipophilic and amphiphilic drugs. The niosomal structure is shown in fig. 2(A). It delivers the medicament in target site with less risk of side effects and toxicity. Surfactant form lipid bilayer when it interacts with the aqueous media. Based on size of niosomes it is classify into 3 types

1. Small Unilamellar Vesicles SUV (0.05-0.5µm)
2. Multi Lamellar Vesicles MLV (0.05µm)
3. Large Unilamellar Vesicles LUV (0.10µm) as shown in fig. 2(B) [2, 3]

**Liposomes**

Liposomes are concentric bilayer vesicles and microscopic in nature, in addition to it, they are capable of loading potent drug along with phospholipids to aim on drug targeting. In Liposomes phospholipids are dispersed in the aqueous solution they rapidly form multi-lamellar concentric bilayer vesicles which are about 0.05-5.0µm diameter as pictured in fig. 3(A). It is also called as micro particulate or colloidal barrier [4].

Based on surface charge, these are of 3 types.

1. Liposomes with positively charged

2. Liposomes with negatively charged

3. Liposomes with neutral charged

Liposomal corneal penetration: Positively liposomes > negatively liposomes > neutral liposome [4].

Based on the vesicle size liposomes are categorized into

1. Multi Lamellar Vesicles (>0.1µm)

2. Small Lamellar Vesicles (0.1µm)

3. Large Lamellar Vesicles (<0.1µm) represented in fig. 3(B) [4]. Structure and components of various types of liposomes are shown in fig. 4.

**Aquasomes**

It is a self assembly of triple layered particles with large surface area. It is also called as “Bodies of water” which acts as protein and peptide carrier. These are spherical in shape with a diameter of 60-300 nm [5]. It has a property of maintaining a conformational reliability with a high degree of exposure to the surface. It protects the fragile biological molecule. Aquasomes uphold molecular confirmation and optimal pharmacological action. It delivers the drug at a specific target site with molecular shielding of contents in a sustained release mechanism. It consists of ceramic core which is surrounded by the polyhydroxy oligomers and the active drug is entrapped in the coating by absorption through ionic and non covalent interaction represented in fig. 5(A) [5].

**Transfersomes (Elastic liposomes)**

These are used in targeted controlled drug delivery system which is ultra flexible and has deformable vesicles less than 300 nm [6]. It can penetrate to a pore to the deeper epidermis layers (i.e. Stratum corneum to stratum bacile) and then enters the systemic circulation for the potential drug delivery. It is composed of buffer solution, dye, small amount of alcohol, surfactant and soya phosphotidyl choline. Surfactant acts as edge activator and increases the permeability across the skin represented in fig. 5(B) [6].

**Invasomes**

It is a liposomal vesicle that is neutrally charged which are capable of deliver both the hydrophilic and lipophilic drugs over deeper layers of epidermis and exhibits its action [7]. They are Great potential carriers for the transdermal skin delivery. It is composed of small amounts of ethanol, terpene or terpene mixtures (1-5%) and Phosphotidyl choline as depicted in fig. 5(C) with increased concentration of terpene in the composition the vesicle size and membrane elasticity increases [8, 24].

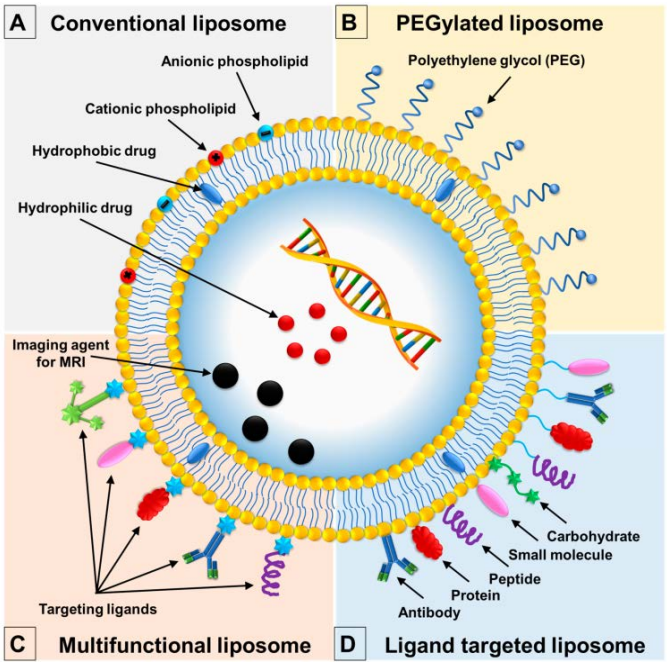


**Fig. 4: Structure and components of various types of liposomes [21, 28, 38, 39, 51]**

### Phytosomes

Phytosomes are a type of herbosomes, which are mainly composed of Phytoconstituents (neutraceuticals such as flavonoids and terpenoids) which ranges from 500 nm-100µm as represented fig. 5(D). It is a complex of lipid molecules that enhances the bio availability, the solubility of the drug and absorption of water soluble Phytoconstituents. It is composed of aprotic solvent, phytoconstituents and phosphotidyl choline. It acts as a potential carrier for anti skin ageing agent and non pathogenic disorders. Phytosomal formulation improves antioxidant property and protects the cardiovascular system from oxygen residues by preventing ischemic heart disease [9].

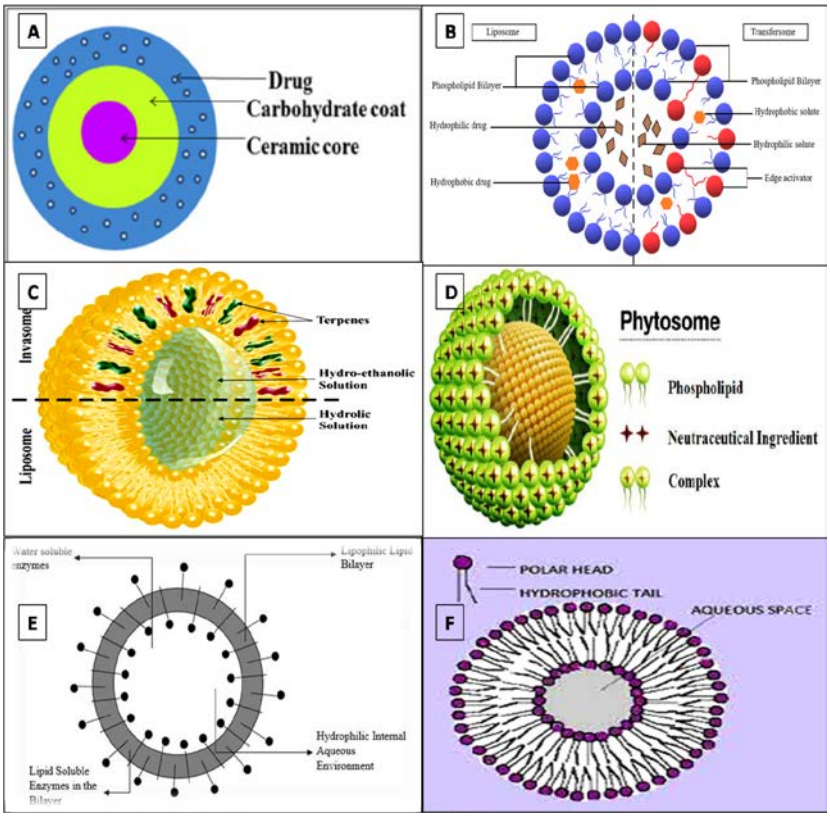


**Fig. 5: (A) Structure of aquasome [53, 46]; (B) Structure of Transferosome and it comparison with Liposome [51, 60]; (C) Structure of Invasome and it comparison with Liposome [8, 24]; (D)Structure of Phytosomes [9, 22, 26]; (E) Structure of Enzymosomes [11]; (F) Structure of sphingosomes [12, 29]**

**Enzymosomes**

Enzymosomes are the enzymes which are encapsulated over the liposomal vesicles and the attachment is mediated by covalent bond/coupled formation as shown in fig. 5(E). These types of vesicles are used for the treatment of targeted drug delivery in tumor cells. This formulation can increase the antitumor activity of drugs. The enzymes which are encapsulated in the liposomal vesicles are β-lactanase, β-glucosidase, carboxy peptidase and alkaline phosphatise. These enzymes pave a way for the following

1. Gene delivery to the tumor cells through the catalysis of the enzymes.
2. Pharmacological action at the specific site.
3. Activation of prodrug. [10, 11]

**Sphingosomes**

Sphingosomes are bilayer concentric vesicles. It was first discovered by University of British Columbia and it was developed by Inex Pharmaceutical Corporation [12]. It is composed of stearyl amine, cholesterol and sphingolipid. The structure of vesicles in the Sphingosomes is similar in liposomal structure as represented in fig. 5(F) but it differs in the composition of phospholipids called as sphingolipid. It maintains drug retention properties and provides stability towards acid hydrolysis. It is administered through the route of intravenous, intramuscular, inhalation, oral and transdermal. Used as carriers for ionotrops, psychotropic's, nucleic acids, lipophilic cations [12].

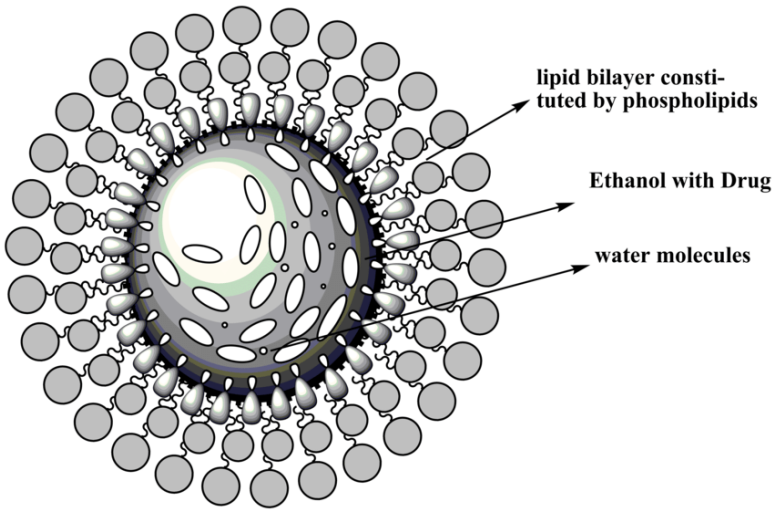


**Fig. 6: Structure of ethosomes [51, 58, 60]**

**Ethosomes**

Lipoidal vesicles with high concentration of ethanol called as Ethosomes. Ethosomes are also known as ethanolic liposomes. The fig. 6 it is a soft and a novel vesicular carriers for the transdermal drug delivery over deeper layers of skin as a controlled release mechanism. It is composed of water, cholesterol, dye, polyglycol, ethanol (20-50%), vehicle, and phospholipids. High concentration of ethanol enhances the ability of drug permeation through skin [13].

**Electrosomes**

Electrosomes are novel surface display system. It is a transmembrane protein. It generates and propagates electrical signals which allow sensing the surroundings. Interaction between a cascade of redox enzymes and scaffolding for multiple releases by oxidation of fuel. It is composed of dockerin containing enzyme which attaches to the cohesive sites of scaffolding to assemble the ethanol oxidation cascade as hybrid anode and dockerin containing oxygen reducing enzyme attached to multiple copies to cohesion bearing scaffolding as hybrid cathode [14]

**Table 1: Types of excipients and their role in somes drug delivery system**

| S. No. | Types | Composition | Role | Reference |
|---|---|---|---|---|
| 1. | Niosomes | a. Nonionic surfactants: Spans and Tweens, Poly hydroxyl groups and Cetyl alcohol. | ➢ 1-10 mmol (1-2.5%).<br>➢ HLB value 4-8.<br>➢ Entrapment efficiency.<br>➢ Drug encapsulation. | 2, 3 |
| | | b. Phospholipids: Dicetyl phosphate, Stearyl amine. | ➢ Helps in the formation of vesicles interact with aqueous media. | |
| | | c. Cholesterol | ➢ Provide proper shape and rigidity for the niosome.<br>➢ Stabilizes permeability bilayer fluidity and stability. | |
| 2. | Liposomes | a. Cholesterol | ➢ Changes in permeability.<br>➢ Effect of particle size. | 4 |
| | | b. Surfactants: Phosphotidyl serine, Phosphotidyl choline. | ➢ May change to different phases based upon transition temperatures. | |
| | | c. Cholesterol: Sterols. | ➢ Decrease the encapsulated drug leakage.<br>➢ Plays major role in bilayer fluidity.<br>➢ Acts as fluidity buffer. | |
| 3. | Invasomes | a. Phosphotidyl choline | ➢ Increasing flexibility of vesicles.<br>➢ Edge activator. | 7, 8, 19 |
| | | b. Terpene | ➢ Increasing lipid bilayers of skin.<br>➢ Increases diffusion of drugs by extracting lipid from SC. | |

| | | | | |
|---|---|---|---|---|
| | | c. Ethanol | ➢ Acts as penetration enhancers.<br>➢ Helps in increasing fluidity.<br>➢ Ability to squeeze through the small pores of skin.<br>➢ Increases stability of vesicles to penetrate over the skin. | |
| 4. | Phytosomes | a. Phospholipids: Phosphatidyl choline (Ionositol, Serine, Ethanolamine)<br>b. Phyto constituents: Terpenoids, Flavanoids<br>c. Aprotic solvents: Ethyl acetate, Methylene chloride, acetone, Dioxane | ➢ Prevents the drug from water triggered degradation.<br>➢ Carrier for both water and fat miscible nutrients.<br>➢ Natural digestive aid.<br>➢ Exhibits Therapeutic action<br>➢ Provides solubility. | 9 |
| 5. | Enzymosomes | a. Enzyme: Alkaline phosphatise, Carboxy peptidase, β-glucosidase, β-lactanase<br>b. Liposomal vesicle: Cholesterol, Surfactant and Phospholipids | ➢ Prodrug activation.<br>➢ Covalent attachment with liposomal vesicle for therapeutic action.<br>➢ Targeted drug delivery. | 10, 11 |
| 6. | Sphingosomes | a. Spingolipid: Ceramide, Sphingosine, Sphingomyelin<br>b. Cholesterol<br>c. Stearyl amine | ➢ Maintenance of drug retention properties.<br>➢ Increases stability to acid hydrolysis.<br>➢ Reduces electrostatic and hydrogen bonding in interaction of vesicles.<br>➢ Increases the stability of sphingolipid. | 12 |
| 7. | Ethosomes | a. Phospholipid: Dipalmityl phosphtidyl choline, Phosphatidic acid, Phosphotidyl choline<br>b. Cholesterol<br>c. Alcohol: Isopropyl alcohol, Ethanol<br>d. Dye: Rhodamine red, Rhodamine-123, Isothiocynate, Fluorescence<br>e. Polyglycol: Transcutol RTM, Propylene glycol<br>f. Vehicle: Carbopol D94 | ➢ Elasticity to vesicles.<br>➢ Formation of vesicles.<br>➢ Stability to vesicles.<br>➢ Creates disturbance of skin lipid bilayer organization.<br>➢ Penetration enhancer.<br>➢ Characterization study.<br>➢ Enhance penetration.<br>➢ For gel former. | 13 |
| 8. | Aquasomes | a. Solid core: Ceramic, diamond, Hydroxylapatite and Calcium phosphate.<br>b. Coating material: Trehalose, cellobiose, Polyhydroxy oligomers, carbohydrates.<br>c. Drug | ➢ Specific targeting.<br>➢ Molecular confirmation.<br>➢ Maintains structural stability.<br>➢ Protects the drug from denaturing effects of pH and temperature.<br>➢ Acts as dehydro protectant.<br>➢ Gives therapeutic action by, non covalent bonds, entropic forces, ionic and vanderwaal forces. | 15, 18 |
| 9. | Transfersomes | a. Surfactant: Dipotassium glycyrrhizinide, Deoxycholate, Span80, Tween 80, Sodium cholate.<br>b. Phospholipid: Soya phosphotidyl choline.<br>c. Alcohol: Methanol, Ethanol.<br>d. Buffer: Saline phosphate buffer (pH6.4)<br>e. Dye: Nil red and Rhodamine 123. | ➢ Increases vesicle deformability, permeability, fluidity.<br>➢ Acts as edge activator.<br>➢ Helps in formation of vesicle complexes.<br>➢ Solvent for solubilisation of drug.<br>➢ Hydrating medium.<br>➢ For study of confocal scanning laser microscopy. | 16, 17 |
| 10. | Electrosomes 14 | a. Hybrid anode: Dockerin containing enzymes of formaldehyde dehydrogenase, Aldehyde dehydrogenase.<br>b. Hybrid cathode: Dockerin containing reducing oxygen enzyme of copper oxidase. | ➢ Assemble ethanol oxidation cascade.<br>➢ Attach to multiple copies to the cohesion bearing scaffolding protein. | 14 |

**Table 2: Formulation methods for preparation of various somes drug delivery system**

| S. No. | Formulation | Types | Procedure | Reference |
|---|---|---|---|---|
| 1. | Hot method | Ethosomes | Phospholipids in water and propylene glycol in ethanol were added and heated separately upto 40 °C and mixed well. Finally the therapeutic agent was added. | 13 |
| 2. | Cold method | Ethosomes | Excipients were added to the ethanol and dissolved by vigorous shaking and heated. At 40 °C propylene glycol was added. Then water was added to it for 5 min with continuous stirring and the particle size is reduced by sonication and extrusion method. This final formulation was stored in refrigerator. | 13 |
| 3. | Preparation of inorganic core, coating with oligomers and drug loading | Aquasomes | *Core preparation:* Ceramic core was fabricated by colloidal precipitation and it is sonicated under ultrasonic bath at 4 °c for 2hr and a precipitate is formed. Precipitated cores are then centrifuged, washed to remove any traces of NaCl formed during the process. Precipitated cores are resuspended in distilled water and then filtered in a fine membrane.<br>$2Na_2HPO_4+3CaCl_2+H_2O \rightarrow Ca_3(PO_4)_2+4NaCl+2H_2+Cl_2+(O)$<br>*Coating:* Cores are dispersed in aqueous solution of coating material and kept for | 18 |

| | | | | |
|---|---|---|---|---|
| | | | sonication and lyophilization for the irreversible adsorption of coating material to the core.<br>*Drug loading:* Finally, the drug was loaded into the coating material through adsorption by dispersing in the suitable buffer solution containing drug at low temperature. | |
| 4. | Sonication | Niosomes<br>Liposomes<br>Aquasomes<br>Sphingosomes | Suspension is taken into the glass vial and subjected to sonication for 5-10 min at 60 °C with the help of sonic energy suspension yields small unilamellar vesicles of 15-50 nm<br>(small volumes-probe type sonicator; large volumes; bath type sonicator) | 20, 21 |
| 5. | Thin film hydration method | Niosomes<br>Liposomes<br>Phytosomes<br>Invasomes<br>Enzymosomes<br>Sphingosomes | Surfactants and cholesterol were solubilized in a round bottomed flask containing organic solvents (chloroform, diethyl ether) and subjected to rotary evaporator for the evaporation of volatile solvent. A thin film is shaped inside the glass walls of the flask. Afterwards the phosphate saline buffer (PBS) was added to it to rehydrate the thin film and allowed to sonication and this lead to the creation of Multilamellar vesicles (MLV). In Enzymosomes, enzymes which are already dissolved in phosphate buffer (pH-5.6) were dispersed in liposomal vesicle suspension for encapsulating enzyme over the vesicles. | 11, 16, 20, 21, 22 |
| | | Transfersomes<br>Invasome | The hydrated thin film suspension was allowed for sonication for the desired size and it is homogenized through the extrusion polycarbonate membrane. Volatile solvents were added to dissolve the contents and then subjected to rotary evaporator for the evaporation of volatile solvents and buffer solution (pH6.5) was added to the lipid film for 1hr at 60 rpm. After 2 h vesicles get swollen at room temperature. Large uniamellar vesicles (LUV) are obtained by this method. (subjected to sonication SUV are obtained with probe type at 40 °c for 30 min, bath type at 500 °c for 30 min). | 11, 16, 20, 21, 22 |
| 6. | Microfluidizer | Niosomes<br>Liposomes<br>Sphingosomes | Drug, surfactants and excipients were pumped into the interaction chamber at a pressure of 100 ml/min; 10,000psi and then passed to the cooling loop for removal of heat during the process and allowed to recirculation until the formation of vesicles attains the desired size. | 21, 23 |
| 7. | Solvent evaporation method | Phytosomes | Drug and phospholipids were refluxed with 20 ml of acetone in a 100 ml round bottomed flask at 50-60 °C for 2hr, then concentrate the suspension to 5-10 ml. A phytosomal precipitate formed it is collected, filtered and dried. | 22 |
| 8. | Reverse evaporation separation method | Niosomes<br>Liposomes<br>Sphingosomes | Surfactant and cholesterol are dissolved in the organic solvents and aqueous buffer and was allowed for sonication for the formation of o/w emulsion and allowed for evaporation of organic solvents by rotary evaporator. This Leads to the formation of viscous gel. To this phosphate buffer was added for hydration and Large unilamellar vesicles were formed. | 23, 25 |
| 9. | Ethanol/Ether injection method | Niosomes<br>Liposomes<br>Sphingosomes<br>Ethosomes | The ethanol/ether solution was injected slowly using a syringe in the aqueous medium containing drug and formulation excipients at 60 °C. It was allowed for heating or subjected to vacuum for the removal of ethanol/ether solution and this leads to the formation of small unilamellar vesicles (SUV) (50-1000 nm)<br>(14 gauge needle for niosomes and 22 gauge needle for liposomes). | 27-30 |
| 10. | Freeze thaw method | Niosomes<br>Liposomes<br>Enzymosomes<br>Sphingosomes | Drug and phospholipids were dissolved in organic solvents and allowed to freeze and dried. Then saline water was added to the formation of vesicles. | 27-30 |

**Table 3: Advantages and disadvantages of types of somes**

| S. No: | Types | Advantages | Disadvantages | Reference |
|---|---|---|---|---|
| 1. | Invasomes | ➢ Compared to iontophoresis and phonophoresis it is a simple transdermal method of drug delivery.<br>➢ Formulated in semisolid (gel) for patient compliance.<br>➢ Formulation, contains non-toxic raw material.<br>➢ Drug delivery by non-invasive technique. | ➢ Reaction of phospholipids causes oxidation/hydrolysis leads to instability of invasomal formulation.<br>➢ The encapsulated drug leads to leakage or fusion.<br>➢ Expensive production cost. | 8, 24 |
| 2. | Enzymosomes | ➢ Increased pharmacological action and prodrug activation<br>➢ Completely biodegradable in nature.<br>➢ Non-toxic nature.<br>➢ Increased stability and encapsulation.<br>➢ More than 1 enzyme moiety is formulated to achieve targeted drug delivery. | ➢ The drug molecule may cause leakage or fusion while encapsulating.<br>➢ Chances of low solubility, reduction in half life leads to reduced bio availability.<br>➢ The phospholipids, which are present in liposomal vesicles may cause hydrolysis and oxidation reactions thus it effect the stability<br>➢ Expensive production cost for formulation of liposomes. | 11 |
| 3. | Sphingosomes | ➢ Passive drug targeting in tumor therapy.<br>➢ Better drug retention properties.<br>➢ Increased circulation time for pharmacokinetic effect.<br>➢ Less risk of toxicity in encapsulating agents.<br>➢ Great potential towards stability in | ➢ Less entrapment efficacy.<br>➢ Expensive production cost. | 12 |

| | | | | |
|---|---|---|---|---|
| | | encapsulation. | | |
| 4. | Ethosomes | ➢ When compared to iontophoresis and phonophoresis ethosomal formulation is a simple method of drug delivery.<br>➢ High patient compliance in semisolid formulation.<br>➢ Possible delivery of large molecules such as proteins and peptides.<br>➢ Ethosomal formulations are widely used in pharmaceutical, veterinary and cosmetic fields.<br>➢ Non toxic in nature. | ➢ Less solubility of the drug in lipophilic and aqueous environments to reach the dermal micro circulation and then to systemic circulation.<br>➢ Slow, sustained drug delivery in bolus type drug input. Excipients and enhancers may cause skin irritation and dermatitis.<br>➢ Product will be loss when transfer from organic to aqueous media.<br>➢ Poor yield. | 13 |
| 5. | Niosomes | ➢ Osmotically stable and active.<br>➢ Improves oral bio availability of soluble drugs.<br>➢ Low doses can achieve target drug delivery.<br>➢ Enhances more stability and economy.<br>➢ More potential and less side effects when compared to other drugs. | ➢ Leakage of entrapped drug takes place.<br>➢ Hydrolysis may take place in entrapping drug.<br>➢ Insufficient drug loading.<br>➢ Aggregation of suspension.<br>➢ Time consuming process. | 31-33 |
| 6. | Transfersomes | ➢ Formulated in the delivery of both systemic and topical application.<br>➢ Protection of encapsulated drug from metabolic degradation.<br>➢ Act as carrier in both low and high molecular weight drugs.<br>➢ Bio compatible and biodegradable in nature.<br>➢ Great penetration of intact vesicles due to high deformability. | ➢ Absence of purity in natural phospholipids.<br>➢ These are chemically unstable due to the predisposition of oxidative degradation.<br>➢ Formulation and manufacturing are expensive. | 34, 35 |
| 7. | Aquasomes | ➢ Great potential in solubility, stability, rapid degradation of drug molecule<br>➢ Improvement of therapeutic efficacy of active agent and less side effects.<br>➢ controlled and target drug delivery in various routes of administration.<br>➢ Used in the various imaging tests. | ➢ Care should be taken in production of carriers<br>➢ Dose dumping is carried out by carriers.<br>➢ Expensive.<br>➢ Leaching and aggregation of prolonged storage. | 36, 37 |
| 8. | Liposomes | ➢ Increased accumulation in the target site.<br>➢ Completely biodegradable.<br>➢ Carriers for controlled and sustained release drugs.<br>➢ Less risk of toxicity.<br>➢ Simple and easy attachment of targeted ligands. | ➢ Problems will arise in repeated i. v administration.<br>➢ Difficulty arises in stability due to short life.<br>➢ Reactivity of phospholipids may occur.<br>➢ Expensive.<br>➢ Poor solubility. | 38-40 |
| 9. | Phytosomes | ➢ Enhances absorption of lipid insoluble polar drugs of oral and topical. Nutritional benefits.<br>➢ Enhanced permeation of phytoconstituents through the skin.<br>➢ Hepatoprotective synergistic effect due to phosphotidyl choline.<br>➢ High entrapment efficiency. | ➢ Phytoconstituents are rapidly eliminated from phytosomes.<br>➢ Phytosomes are sensitive the pH of phospholipids.<br>➢ Leaching of phytoconstituents leads to reduced therapeutic action and unstable in nature. | 41, 42 |

**Table 4: Evaluation parameters of various somes**

| S. No: | Evaluation parameters | Somes type | Method used | Instrument used | Reference |
|---|---|---|---|---|---|
| 1. | Morphology/vesicle shape | Niosomes<br>Aquasomes<br>Transfersomes<br>Phytosomes<br>Invasomes<br>Sphingosomes<br>Ethosomes | Microscopy | Scanning electron microscopy (SEM), Transmission electron microscopy (TEM). | 35-45 |
| | | Liposomes | Freeze fracture technique | Freeze fracture electron microscopy, Freeze-etch electron microscopy. | |
| 2. | Particle size | Liposomes<br>Enzymosomes | Unimodel method of data processing | Quassi elastic light scattering | 48-51 |
| | | Niosomes<br>Aquasomes<br>Phytosomes<br>Invasomes<br>Ethosomes | Size distribution rate, dynamic light scattering | Optical microscopy, Nanosizer, Particle size analyzer | 48-51 |
| 3. | Zeta potential | Niosomes<br>Aquasomes<br>Phytosomes<br>Invasomes<br>Enzymosomes<br>Ethosomes | Photon co relation spectroscopy | Malvern zeta sizer,<br>Zeta sizer Beckmann coulter | 52-56 |

| | | | | | |
|---|---|---|---|---|---|
| 4. | Drug entrapment efficiency<br>Entrapment efficiency | Niosomes<br>Aquasomes<br>Transfersomes<br>Phytosomes<br>Invasomes<br>Sphingosomes<br>Ethosomes | Exhaustive dialysis, centrifugation and Ultra centrifugation | UV spectrophotometry, HPLC | 57-61 |
| | | Liposomes | Protamine aggregation method | Mini column centrifugation. | |
| 5. | Invitro drug release | Niosomes<br>Liposomes<br>Invasomes<br>Sphingosomes | Osmotic Diffusion | Dialysis membrane<br>Dialysis tube, Franz Diffusion cell | 62-66 |
| | | Aquasomes<br>Transfersomes<br>Ethosomes | Incubation | Cellophone membrane,<br>UV spectrometry, HPLC, HPTLC | |
| 6. | Surface charge | Liposomes<br>Transfersomes<br>Enzymosomes<br>Ethosomes | Electrophoresis | Dynamic light scattering (coulter), Zeta sizer. | 67, 68 |
| 7. | Mean particle diameter | Niosomes | Mean particle diameter | Photomicroscopy(1000x) | 69-71 |
| 8. | Penetration | Transfersomes<br>Invasomes<br>Sphingosomes<br>Ethosomes | Florescence marker | Confocal scanning laser microscopy(CSLM) | 16 |
| 9. | Turbidity | Transfersomes | Observation | Nephelometer | 16 |

**Table 5: Applications of various somes in drug delivery system**

| S. No. | Types of somes | Applications | Reference |
|---|---|---|---|
| 1. | Enzymosomes | ➢ Used in formulating anti-inflammatory, breast cancer and metastases drugs.<br>➢ Gene delivery to the tumor cells.<br>➢ Used for formulating antitumor drugs as enzymosomes increased its action potential. | 11 |
| 2. | Sphingosomes | ➢ Used for Treatment of thromboembolic disease in rabbits.<br>➢ Used in anti microbial drugs, anti fungal drugs and viral therapy.<br>➢ Enzymes such as Sterptokinase urokinase esterase are prepared in spingosomal vesicles.<br>➢ Used for Formulating the drugs which are used for tumor therapy.<br>➢ It is compatible with skin, hence sphingosomes are used in the cosmetic industry. | 12, 29 |
| 3. | Ethosomes | ➢ Antiviral drugs such as Acyclovir is formulated using ethosomes is used topically to treat Herpes Labialis.<br>➢ Cannabidol is formulated using ethosomes for the treatment of rheumatic diseases.<br>➢ Ethosomes enhances greater permeation of ferulic acid through the stratum corneum epidermal barrier.<br>➢ Hormones are formulated using ethosomes and administered transdermally to protect from the first pass effect in oral formulation.<br>➢ Ethosomes are formulated in oral drug delivery of biogenic molecules For therapeutic efficiency and permeation. | 13 |
| 4. | Electrosomes | ➢ Ear targeting<br>➢ Muscle targeting.<br>➢ Nervous system targeting.<br>➢ For brain targeting formulations.<br>➢ Propagates and generates electrical signal that allows sensing the surroundings. | 14 |
| 5. | Aquasomes | ➢ Multilayered core (5 layers) is used as targeted intracellular gene therapy.<br>➢ Used as Immuno adjuvant for proteinaceous antigens.<br>➢ Haemoglobin is formulated in hydroxyl apatite (core) coated with trehalose treated as an oxygen carrier.<br>➢ Formulation of chitosan coated Serratiopeptidase in oral drug delivery.<br>➢ Pyridoxal-5-phosphate coated insulin shows good response in parenteral delivery. | 18 |
| 6. | Invasomes | ➢ Formulation of curcumin using invasomes increases the solubility and bio availability of the drug.<br>➢ To control tyrosinase activity for hyper pigmentation disorders phenylethyl resorcinol loaded invasomes are used.<br>➢ Isradipine loaded invasomes is used for transdermal delivery of hypertension. | 19, 24 |
| 7. | Niosomes | ➢ Localized and encapsulated drugs with niosomes are used to treat tumours.<br>➢ Potent target drug delivery in Reticulo endothelial system (RES).<br>➢ Used in Formulation of anticancer drugs, Tuberculosis drugs, Leishmania, inflammatory and hormonal drugs.<br>➢ Used in the encapsulation of Colchines, Estradiol, Tretion, Dithranol.<br>➢ In transdermal application it protects the drug from hepatic first pass effect. | 72-76 |
| 8. | Transfersomes | ➢ Induces Great transdermal immunization in transcutaneous hepatitis-B vaccines.<br>➢ Shows good immune response in human serum albumin/gap junction.<br>➢ Targeted delivery of insulin to systemic circulation, which is equivalent to subcutaneous | 77-79 |

| | | | |
|---|---|---|---|
| | | injection.<br>➢ Used as carriers for steroids, NSAIDS, anticancer drugs, local anaesthetics.<br>➢ Formulated in vaccines, steroids, protein and peptide delivery across the skin.<br>➢ Exhibit great potential in drug delivery across the deeper layers of skin. | |
| 9. | Phytosomes | ➢ Shows greater potential in cosmetics as anti skin ageing agent and cosmetics that treats non pathogenic skin conditions.<br>➢ Therapeutically used in the formulation of cardiovascular, anti inflammatory, anticancer drugs.<br>➢ Used in the transdermal application of inflammation, toxicities, weight loss, cancers, chronic and acute degenerative disorders.<br>➢ Influences great bio availability and absorption of water soluble drugs. | 80-83 |
| 10. | Liposomes | ➢ Monoclonal antibody directed liposome is used as vectors For genetic transfaction.<br>➢ In ocular delivery, approved drug Verteporfin (liposome) is used.<br>➢ Used in small cytotoxic molecules in tumour therapy.<br>➢ Carriers for antineoplastic drugs, anti microbial drugs, chelating agents, steroids, vaccines, genetic materials.<br>➢ Role in formulation of potent drug for therapeutic action. | 84 |

**Table 6: Patents of various somes (2018-20)**

| S. No. | Type of somes | Title | Author | Publication no./ Year of publication |
|---|---|---|---|---|
| 1. | Niosomes | Preparation for Mortellaro's disease treatment | Belyakova Natalya, Aleksandrovna, Bodrova yulya yurevna, Dorofeev Andrej fedorovich, Kovalenko anatoliz, Mikhajlovich, Kurbanov rusllan zamirovich,Yavnikov nazar valentinovich, Zuev nikolaj petrovich | RU2720231C1/ 2020 |
| | | Preparing method for positively electrified charged niosome, and charged niosome | Brian charles keller, Kodama akira, Miyoshi tatsuro | US20190091153A1/ 2019 |
| | | Topical composition comprising plant extracts | Pacchetti Barbara | AU2017243956A1/ 2018 |
| 2. | Liposomes | Formulation comprising liposomes | Hata katsura, Hird Geoff, Ishihara hiroshi, Muto hiroki | W02020129826A1/ 2020 |
| | | Liposomes comprising sphingomyelin | Halbherr Stefan | W0201922220A1/ 2019 |
| | | Cataplasm mask containing flexible nano liposomes | Chen hanyang, Luo jiaming, Qui xiaofeng, Zhou Zhigang | CN107693381A/ 2018 |
| 3. | Aquasomes | Gel formulation for treating diabetic foot ulcer | Uma Shankar marakanam, Srinivasan | US2020188314A1/ 2020 |
| | | Topical compositions for stimulating hair growth | Brichtla lars | W02019236596A1/ 2019 |
| | | Acoustic field coupling with micro-devices | Freitas JR Roberta, Hogg tad | US10024950B1/ 2018 |
| 4. | Phytosomes | Composition for prevention or treatment of skin inflammation comprising centella asiatica phytosome and Mori Radicis cortex extract | Jang jun sung, Kim has sung, Myung pyung kelin, Park ju ho, Park mork soon | KR102073009B1/ 2020 |
| | | Method of producing nanoscale phytosome system | Kezimana parfe, Marakhova anna igrevna, Shvitko boris semenovich, Smagulova dilda, Stanshevskij yaroslav mikhalovich | RU2680809C2/ 2019 |
| | | A carrier for pulverization of oils, fatty acids and hydrophobic substances | Beran milos, Drahorad Josef, Hromadka Robert, Vltasvsky ondrej | CZ31574VU1/ 2018 |
| 5. | Ethosomes | Liposomes and ethosomes charged with Rosmarinic acid suitable for use in cosmetics | Karatoprak gokche, Yucel cigdem | W02020117163A1/ 2020 |
| | | Method of preparing bioactive substance encapsulated ethosome | Jang gi hyun, Kim yu mi, Oh ga hee, Park young jun | W02019004563A1/ 2019 |
| | | Active skin care composition and application | Chen jianhuan, Chen songbin, Liu jiesen, Luo yao, Ni yanyan | CN107550847A/ 2018 |
| 6. | Transfersomes | Lipid compositions containing bioactive fatty acids | Berger Alvin, remmereit jan | US10537542B2/ 2020 |
| | | Preparation of multi-layer Transfersomes containing linoleic acid and alpha-linoleic acid ester complexes using organic acid hydrolysis and fatty acid esterification from flax seeds | Yoo dong min | KR102008266B1/ 2019 |
| | | Aripiprazole compositions and methods for transdermal delivery | Hossain muhammed anwar, Plakogiannis fotios M | CN107929239A/ 2018 |
| 7. | Invasome | Ibuprofen nanoparticle carriers encapsulated with hermetic surfactant films | Morrison eric. | US10561627B2/ 2020 |
| | | Bacteria based protein delivery | Arrieumeriou Cecile, lttig simon | EP3145946B1/ 2019 |
| | | Therapeutic agents for skin diseases and conditions | Vander jagt david L, Deck Lorraine M, Royer Robert E, Heidrich john E | US9925153B2/ 2018 |
| 8. | Sphingosom | Targeted therapeutics | Jain neera, Ying weiwen, Chimmanamada | WO2018236781A3/ |

| | | | |
|---|---|---|---|
| e | | dinesh, Zhang junyi, Kale amit | 2020 |
| | Therapeutic elastic bandage for modulating the endocannabinoid system | Erbst steven Robert, Erbst Cameron Patrick, Weber Mathew lee | WO2019194871A1/ 2019 |
| | Elastomeric articles having skin care properties and methods for their production | Foo khon pu, Lim chin keong | AU2017279818A1/ 2018 |

**Table 7: Report on various route of administration of Somes and its importance**

| S. No. | Type of Somes/Carrier | Route of administration | Reason | Reference |
|---|---|---|---|---|
| 1. | Liposomes | Topical route of administration by using Triamcinolone as a model drug | Liposomes alter the Triamcinolone arrangement and induce local rather than systemic effects. | 85 |
| 2. | Niosomes | Ocular delivery by using Cyclopentolate as drug | As compared to other somes, niosomes are used as a successful carrier for cyclopentolates. | 86 |
| 3. | Aquasomes | Oral delivery of enzymes like Serratiopeptidase | Serratiopeptidase acts against inflammation. The key reason for using aquasomes as carrier is because of its property of preserving the bioactive molecules' conformational integrity. It shows that aquasomes have the ability to bear the pharmaceutical related peptide. | 87 |
| 4. | Transfersomes | Non-invasive topical delivery of antigen(Tetanus toxoid)/topical immunization | Transfersomes is a more efficient non-invasive topical delivery of tetanus toxoids compared to niosomes and liposomes that cause weaker immune responses. | 88 |
| 5. | Invasomes | Transdermal delivery of isradipine | The prepared Isradipine loaded invasomes deliver ameliorated flux show better trap efficiency and transdermal delivery efficiency and reduced hypertension compared to the other somes carrier. | 89 |
| 6. | Phytosomes | Oral route of administration by using silymarin (flavonoid complex obtained from milk thistle) | Silymarin is a heptoprotective agent resulting in decreased bioavailability due to its low solubility in both water and oil, and low intestinal permeability. To overcome this problem, phytosomes loaded with silymarin are produced to improve protection and stability in the bioavailability. | 90 |

**Table 8: Report on marketed products of various somes**

| S. No. | Type of somes | Marketed product | Active drug | Company and manufacturer |
|---|---|---|---|---|
| 1. | Niosomes | Lancome® | Antiageing agent | Loreal, Paris |
| 2. | Liposomes | DaunoXome® | Daunorubicin | Galen limited, United Kingdom |
| | | DepoCyt® | Cytarabine | Pacira pharmaceuticals Inc. California, USA |
| | | Mifamurtide® | Mepact | Takeda pharmaceuticals, Tokyo, Japan |
| 3. | Ethosomes | Decorin cream® | Antiageing agent | Genome cosmetics, USA |
| | | Nanominox® | Minoxidil | Sincere, Germany |
| | | Supravir cream® | Acyclovir | Triama, Isreal |
| 4. | Phytosomes | Sllybin phytosome® | Sllybin from Sllbium marianum | Thorne research Inc., New York |
| | | Haw thorn phytosome® | Vitexin | Swason ultra, North Dokata |
| | | Glinko select phytosome® | Flavonoids from Glinko biloba | Natural factors, Canada |
| 5. | Sphingosomes | Marqibo ™ | Vincristine | Eli Lily, India |
| | | Navelbine ® | Vinorelbine | Glaskosmithkline, England |
| | | Hycumtin ® | Topotecan | Glaskomithkline, England |

## CONCLUSION

Nanosomes carrier are well known for their potential application. There are various types of nanosomes carrier available, for example liposomes, which act as a superior carrier since it as the capacity to encapsulate both hydrophilic and lipophilic drug to defend from degradation. The nanosomes can be manufactured by number of method which based upon the property of the drug molecule. The drug which is present in the nanosomes administrated by numerous routes which include intravenous, oral inhalation, transdermal for the treatment of various diseases and it is also helpful to surmount the certain drawbacks related with drug moiety such as stability, degradation, side effect and bioavailability by incorporating the drug into the nanosomes.

## ACKNOWLEDGEMENT

All authors are very much thankful to the management of Sri Venkateswara College of Pharmacy, RVS nagar, Chittoor, India for their motivation to perform this review in a successful manner.

## FUNDING

Nil

## AUTHORS CONTRIBUTIONS

All the authors have contributed equally.

## CONFLICTS OF INTERESTS

Declared none

## REFERENCES

1. Narasimha Rao B, Ravindra Reddy K, Mounika B, Rahath Fathima S, Tejaswini A. Vesicular drug delivery system: a review. Int J Chemtech Res 2019;12:39-53.
2. Kaur Dhanvir, Kumar Sandeep. Niosomes: present scenario and future aspects. J Drug Delivery Ther 2018;8:35-43.
3. Saeid Moghassemi, Afra hadjizadeh. Nano-niosomes as nanoscale drug delivery systems: an illustrated review. J Controlled Release 2014;185:22-36.

4. Amarnath Sharma, Uma Sharma S. Liposomes in drug delivery: progress and limitations. Int J Pharm 1997;154:123-40.
5. Sanjay Saha, Anupam Sarma, Pranjal Saikia, Tapash Chakraborty. Phytosomes: a brief overview. SAJP 2013;2:12-20.
6. Inde Virbhadra V, Jangme CM, Chavan DV. A review on transferosome: is a boon to human life. IRJPBS 2013;3:174-9.
7. Mohd Kamran, Abdul Ahad, Mohd Aqil, Syed Sarim Imam, Yasmin Sultana, Asgar Ali. Design, formulation and optimization of novel soft nano-carriers for transdermal olmesartan medoxomil delivery; *In vitro* characterization and *in vivo* pharmacokinetic assessment. Int J Pharm 2016;505:147-58.
8. Lakshmi PK, Kalpana B, Prasanthi D. Invasomes-novel vesicular carriers for enhanced permeation. Sys Rev Pharm 2013;3:26-30.
9. Surendra Tripathy, Dilip K Patel, Lipika Baro, Suresh K Nair. A review on phytosomes, their characterization, advancement and potential for transdermal application. J Drug Delivery Ther 2013;3:147-52.
10. Yallappamaharaj R Hundekar, Basavaraj Nanjwade K, Anas Mohameid S, Nagi Idris F, Teerapol Srichana, Azam Sharif Md shafloul. Nanomedicine to tumor by enzymosomes. J Nanotechnol Nanomed Nanobiotechnol 2015;2:4.
11. Shefrin S, Sreelaxmi CS, Vishnu Vijayan, Sreeja C Nair. Enzymosomes: a rising effectual tool for targeted drug delivery sytem. Int J Appl Pharm 2017;9:1-9.
12. Swarnalata Saraf, Paliwal S, Shailendra Saraf. Sphingosomes a novel approach to vesicular drug delivery. Int J Curr Sci Res 2011;1:63-8.
13. Divya Aggarwal, Ujjwal Nautiyal. Ethosomes: a review. Int J Med Res Pharm Sci 2016;4:354-63.
14. Alon Szczupak, Dror Aizik, Sarah Morais, Yael Vazana, Yoav Barak, Edward A Bayer, *et al*. The electrosomes: a surface-displayed enzymatic cascade in a biofuel cell's anode and a high density surface-displayed biocathodic enzyme. Nanomaterials 2017;7:153.
15. Chinmaya Keshari Sahoo, Venkata Ramana D, Satyanarayana K, Dibyalochan mohanty. Drug delivery through aquasomes. J Adv Res 2018;1:156-62.
16. Kulkarni PR, Yadav JD, Vaidya KA,Gandhi PP. Transfersomes: an emerging tool for transdermal drug delivery. Int J Pharm Sci Res 2011;2:735-41.
17. Dharmendra Solanki, Lalit Kushwah, Mohit motiwale, Vicky Chouhan. Transferosomes-a review. World J Pharm Pharm Sci 2016;5:435-49.
18. Inde Virbhadra, Jangme CM, Patil SS, Inde GS, Chavan DV, Yedale AD, *et al*. A review on aquasomes: a potential drug delivery carrier. Int Res J Pharm Appl Sci 2013;3:124-9.
19. Soraya Babaie, Aziizeh Rahmani Del Bakshshayesh, Ji Won Ha, Hamed Hamishekar, Ki Hyun Kim. Invasome: a novel nanocarrier for transdermal drug delivery. Nanomaterials 2020;10:341.
20. Shuo Chen, Sara Hanning, James Falconer, Michelle Locke, Jingyuan wen. Recent advances in non ionic surfactant vesicles niosomes: fabrication, characterization, pharmaceutical and cosmetic applications. Eur J Pharm Biopharm 2019;144:18-39.
21. Maherani B, Arab-tehrany E, Mozafari MR, Gaiani C, Linder M. Liposomes: a review of manufacturing techniques and targeting strategies. Curr Nanosci 2011;7:436-52.
22. Harshal Ashok Pawar, Bhagyashree Dilip Bhangale. Phytosomes as a novel biomedicine: a micro encapsulated drug delivery system. J Bioanal Biomed 2015;7:6-12.
23. Pranshu Tangri, Shaffi Khurana. Niosomes: formulation and evaluation. Int J Biopharm 2011;2:47-53.
24. Nina Dragicevic Curic, Dietrich Scheglmann, Volker Albrecht, Alfred Fahr. Development of different temporfin-loaded invasomes-novel nanocarriers of temoporfin: characterization, stability and *in vitro* skin penetration. Colloids Surf B 2009;70:198-206.
25. Sriram Vemuri, Rhodes CT. Preparation and characterization of liposomes as therapeutic delivery systems. A review. Pharm Acta Helv 1995;70:95-111.
26. Sanjib Bhattacharya. Phytosomes: the new technology for enhancement of bio availability of botanicals and neutraceuticals. Int J Health Res 2009;2:225-32.
27. El-Ridy MS, Abd Elrahman AA, Awad GM, Khalil RM, Younis MM. *In vitro* and *in vivo* evaluation of niosomes containing celecoxib. Int J Pharm Sci Res 2014;5:4677-88.
28. Louise A Meure, Neil R Fariba, Fariba Dehgani. Conventional and dense gas techniques for the production of liposomes: a review. AAPS PharmSciTech 2008;9:798-809.
29. Ashok K, Rajendra Kumar A, Sreekanth Nama, Brahmaiah B, Prasanna kumar Desu, Chandu Babu Rao. Sphingosomes: a novel vesicular drug delivery system. Int J Pharma Bio Sci 2013;2:305-12.
30. Jessy Shaji, Rinki Bajaj. Transethosomes: a new prospect for enhanced transdermal delivery. Int J Pharm Sci Res 2018;9:2681-5.
31. Biswal S, Murthy PN, Sahu J, Sahoo P, Amir F. Vesicles of non-ionic surfactants (niosomes) and drug delivery potential. IJPSN 2008;1:1-9.
32. Peeyush Bhardwaj, Purnima Tripathi, Rishikesh Guptha, Sonia Pandey. A review of niosomal research in the last decade. J Drug Delivery Sci Technol 2020;56:101581.
33. Kumar Abhinav, Pal Jogender Lal, Jaiswal Amit, Singh Vishwabhan. Review of niosomes as novel drug delivery system. Int Res J Pharm 2011;202:61-5.
34. Roopesh Sachan, Tarun Parashar, Soniya, Gaurav Singh, Vishal Singh, Satyanand Tyagi, *et al*. Drug carrier transferosomes: a novel tool for transdermal drug delivery system. IJRDPL 2013;2:309-16.
35. Modi CD, Bharadia PD. Transfersomes: new dominants for transdermal drug delivery. Am J Pharm 2012;2:71-91.
36. Shahabade Gururaj S, Bhosale Ashok V, Mutha swati S, Bhosale Nilesh R, Khade Prashant H, Bhadane Nishant P, Shinde Sagar T. An overview on nanocarrier technology-aquasomes. J Pharm Res 2009;2:1174-7.
37. Marakanam S, Umashankar, Rajesh K Sachdeva, Monica Gulati. Aquasomes: a promising carrier for peptides and protein delivery. Nanomed Nanotechnol 2016;6:419-26.
38. Kataria Sahil, Sandhu Premjeet, Bilandi Ajay, Akanksha Midha, Kapoor Bhawna. Stealth liposomes: a review. IJRAP 2011;2:1534-8.
39. Sharma Shailesh, Sharma Neelam, Kumar Sandeep, Guptha GD. Liposomes: a review. J Pharm Res 2009;2:1163-7.
40. Samad A, Suktana Y, Aqil M. Liposomal drug delivery sytems: an update review. Curr Drug Delivery 2007;4:297-305.
41. Merve Karpuz, Mine Silindir Gunay, Yekta Ozer A. Liposomes and phytosomes for phyto constituents. Advances in the development of novel carriers for bio activities and biological agents; 2020. p. 525-53.
42. Arun Kumar, Bimlesh Kumar, Sachin Kumar Singh, Barinder Kaur, Saurabh Singh. A review on phytosomes: novel approach for herbal phytochemicals. Asian J Pharm Clin Res 2017;10:41-7.
43. Shirsand SB, Para MS, Nagendra Kumar D, Kanani KM, Keerthy D. Formulation and evaluation of ketoconazole niosomal gel drug delivery system. Int J Pharm Investig 2012;2:201.
44. Akshay Singha Roy, Sudipta Das, Arnab Samanta. Design, formulation and evaluation of liposome containing Isoniazid. Int J Appl Pharm 2018;10:52-6.
45. Tawheed Amin, Suman Vikas Bhat. A review on phytosome technology as a novel approach to improve the bio availability of neutraceuticals. IJOART 2012;1:1-5.
46. Neha Narang. Aquasomes: self assembled systems for the delivery of bio active molecules. Asian J Pharm Sci 2012;6:95-100.
47. Srinivas S, Anand Kumar Y, Hemanth A, Anitha M. Preparation and evaluation of niosomes containing aceclofenac. Dig J Nanomater Bios 2010;5:249-54.
48. Lorena Tavano, Luigi Gentile, Cesaro Oliviero Rossi, Rita Muzzalupo. Novel gel-niosomes formulations as multicomponent systems for transdermal drug delivery. Colloids Surf B 2013;110:281-8.
49. Mukul Ashtikar, Kalpa Nagarsekar, Alfred Fahr. Transdermal delivery from liposomal formulations-evolution of the technology over the last three decades. J Controlled Release 2016;242:126-40.
50. Emeline Rideau, Rumiana Dimova, Petra Schwille, Frederick R Wurm, Katharina landfester. Liposomes and polymerosomes: a comparative review towards cell mimicking. R Soc Chem 2018;47:8572-610.

51. Sameh Hosam Abd El-Alim, Ahmed Alaa kaseem, Mona Basha, Abeer salama. Comparative study of liposomes, Ethosomes and transferosomes as carriers for enhancing the transdermal delivery of diflunsial: *in vitro* and *in vivo* evaluation. Int J Pharm 2019;563:293-303.
52. Suna Erdogan, Yekta Ozer A, Hasan Bilgili. *In vivo* behaviour of vesicular urokinase. Int J Pharm 2005;295:1-6.
53. Vishal Sutariya, Parth Patel. Aquasomes: a novel carrier for drug delivery. Int J Pharm Sci Res 2012;3:688-94.
54. Mohammad Houshmand, Francesca Garello, Paola Circosta, Rachele Stefania, Silvio Aime, Giuseppe Saglio, *et al*. Nano carriers as magic bullets in the treatment of leukemia. Nanomaterials 2020;10:1-29.
55. Rathapon Asasutjari, Chittima Managit, Teva Phanaksri, Worapapar Treeesuppharat, Asira fuongfuchat. Formulation development and *in vivo* evaluation of transferin-conjugated liposomes as a carrier of ganciclovir targeting the retina. Int J Pharm 2020;577:119084.
56. Sritoma Banerjee, Kalyan Kumar Sen. Aquasomes: a novel nanoparticulate drug carrier. J Drug Delivery Sci Technol 2018;43:446-52.
57. Sanjay S Jain, Pramod S Jagtap, Neha MD, Kisan R Jadhav, Vilasarao J Kadam. Aquasomes: a novel drug carrier. J Appl Pharm Sci 2012;2:184-92.
58. Ainbinder D, Paolin D, Fresta M, Touitou E. Drug delivery applications with ethosomes. J Biomed Nanotech 2010;6:558-68.
59. Rudra Pratap Singh, Gangadharappa HV, Mruthunjaya K. Phytosomes complexed with chitosan for gingerol delivery in the treatment of respiratory infection: *in vitro* and *in vivo* evaluation. Eur J Pharm Sci 2018;122:214-29.
60. Ascenso A, Raposo S, Batista C, Cardoso P, Mendes T, Praca F, *et al*. Development, characterization and skin delivery studies of related ultra deformable vesicles: transfersomes, ethosomes and transethosomes. Int J Nanomed 2015;10:5837-51.
61. Aman Parashar. Literature review on aquasomes-a drug carrier system. Indian J Med Res Pharm 2017;4:27-30.
62. Srinivas Lankalapalli, Madhupriya Damuluri. Sphingosomes: applications in targeted drug delivery. Int J Pharm Chem Boil Sci 2012;2:507-16.
63. Fathima KM, Antony Nitheesh, Asha Paul, Sreeja C Nair. Sphingosome vesicular system. Int J Pharm Sci Res 2016;39:208-13.
64. Mahale NB, Thakkar PD, Mali RG, Walunj DR, Chaudhari SR. Niosomes: novel sustained release non-ionic stable vesicular systems-an overview. Adv Colloid Interface Sci 2012;183-184:46-54.
65. Manivannam Rangaswamy, Balasubramanian Ayyaswamy, Senthil Kumar Raju, Sandeep Gummadevelly, Sanaullah Shaik. Formulation and *in vitro* evaluation of niosome encapsulated acyclovir. J Pharm Res 2008;1:163-6.
66. Maral Mazloumi Tabrizi, Seyed Ahmad Hosseini, Azim Akbarzadeh Khiyavi. Composition and structure of protein bodies and spherosomes isolated from ungerminated seeds of sorghum bicolour (Linn.) moench. Plant Physiol 1975;55:1-6.
67. Uhumwangho MU, Okor RS. Current trends in the production and biomedical applications of liposomes: a review. J Biomed Sci 2005;4:9-21.
68. Mirna Sherry, Catherine Charcosset, Hatem Fessi, Helene Greige Gerges. Essential oils encapsulated in liposomes: a review. J Liposome Res 2013;23:268-75.
69. Rita Muzzalupo, Lorena Tavano, Roberta Cassano, Sonia Trombino, Teresa Ferrarelli, Nevio Picci. A new approach for the evaluation of niosomes as effective transdermal drug delivery systems. Eur J Pharm Biopharm 2011;79:28-35.
70. Priya Hanu, Singh Harmanpreet. Formulation and evaluation of niosomes containing punicalagin from peels of Punica granatum. J Drug Delivery Ther 2012;2:56-67.
71. Shymala Bhaskaran, Panigrahi L. Formulation and evaluation of niosomes using different non-ionic surfactants. Indian J Pharm Sci 2002;64:63-5.
72. Sepideh Khoee, Morteza Yaghoobian. Niosomes: a novel approach in modern drug delivery systems. Nanostructures Drug Delivery; 2017. p. 207-37.
73. Agarwal R, Katare OP, Vyas SP. Preparation and *in vivo* evaluation of niosomal delivery systems for antipsoriatic drug dithranol. Int J Pharm 2001;228:43-52.
74. Alemayehu Tarekegn, Nisha M Joseph, Palani S, Anish Zacharia, Zelalem Ayenew. Niosomes in targeted drug delivery: some recent advances. Int J Pharm Sci Res 2010;1:1-8.
75. Madhav NVS, Saini. Niosomes: a novel drug delivery system. Int J Res Pharm Chem 2011;1:498-511.
76. Xingli Zhou, Ying Hao, Liping Yuan, Sushmita Pradhan, Krista Shrestha, Ojaswi Pradhan, *et al*. Nano-formulations for transdermal drug delivery: a review. Chin Chem Lett 2018;29:1713-24.
77. Irina Gheorghe, Crina Saviuc, Bianca Ciubuca, Veronica Lazar, Mariana Carmen Chifiriuc. Nanodrug delivery systems for transdermal drug delivery. Nanomaterials Drug Delivery Ther 2019;8:225-44.
78. Nina Dragicevic, Howard Maibach. Combined use of nanocarriers and physical methods for percutaneous penetration enhancement. Adv Drug Delivery Rev 2018;1:58-84.
79. Heather AE Benson. Transfersomes for transdermal drug delivery. Expert Opin Drug Delivery 2006;3:727-37.
80. Bhuwanendra Singh, Rajendra Awasthi, Arshad Ahmad, Asif Saifi. Phytosomes: most significant tool for herbal drug delivery to enhance the therapeutic benefits of phyto constituents. J Drug Delivery Ther 2018;8:98-102.
81. Abdul Azeez N, Sudarshana Deepa V, Sivapriya V. Phytosomes: emergent promising nano vesicular drug delivery system for targeted tumor therapy. Adv Nat Sci Nanosci 2018;9:1-7.
82. Ajay Semalty, Mona Semalty, Rawat MSM. The phyto-phospholipid complexes-phytosomes: a potential therapeutic approach for herbal hepatoprotective drug delivery. Pharmacogn Rev 2007;1:369-74.
83. Babak Ghanbarzadeh, Afshin Babazadeh, Hamed Hamishehkar. Nano-phytosome as a potential food-grade delivery system. Food Biosci 2016;15:126-35.
84. Theresa M Allen, Pieter R Cullis. Liposomal drug delivery systems: from concept to clinical applications. Adv Drug Delivery Rev 2012;65:36-48.
85. Mezei M, Gulasekharam V. Liposomes-a selective drug delivery system for the topical route of administration lotion dosage form. Life Sci 1980;26:1473-7.
86. Azeem A, Anwer MK, Talegaonkar S. Niosomes in sustained and targeted drug delivery: some recent advances. J Drug Target 2009;17:671-89.
87. Umashankar MS, Sachdeva RK, Gulati M. Aquasomes: a promising carrier for peptides and protein delivery. Nanomed Nanotech 2010;6:419–26.
88. Gupta PN, Mishra V, Rawat A. Non-invasive vaccine delivery in transfersomes, niosomes and liposomes: a comparative study. Int J Pharm 2005;293:73-82.
89. Qadri GR, Ahad A, Aqil M, Imam SS, Ali A. Invasomes of isradipine for enhanced transdermal delivery against hypertension: formulation, characterization, and *in vivo* pharmacodynamic study. Artif Cells Nanomed Biotechnol 2017;45:139-45.
90. Maryana W, Rachmawati H, Mudhakir D. Formation of phytosome containing silymarin using thin layer-hydration technique aimed for oral delivery. Materials Today: Proceedings 2016;3:855–66.