INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

NOVEL VESICULAR DRUG DELIVERY SYSTEMS: A REVIEW

Ganesh Sai Myneni*, G. V. Radha, G.V. R. L. Soujanya
GITAM Institute of Pharmacy, GITAM (Deemed to be University), Rushikonda, Visakhapatnam, Andhra Pradesh, India – 530045.

ARTICLE INFO

Article history
Received 24/03/2021
Available online
10/05/2021

Keywords
Vesicular Drug Delivery System,
Lipoidal Bio-Carriers,
Non-Lipoidal Bio-Carriers.

ABSTRACT

This review intends to assess the possibilities of novel vesicular drug delivery systems for targeting. Novel drug delivery seeks to either sustain drug action at a predetermined rate or maintain an adequately constant, adequate drug level in the body with associated minimization of unwanted side effects. An NDDS delivers drugs at a fixed rate decided as per the body's requirement, pharmacological aspects, drug profile, and physiological conditions. In present conditions, not a single novel drug delivery system acts ideally with fewer side effects. The vesicular system's aim in drug delivery has changed the definition of diagnosis and treatment in different biomedical field aspects "A vesicular drug delivery system is the system in which the protection of active ingredients in a vesicular structure which bridges the gap between ideal and availability of novel drug delivery system." Several vesicular drug delivery systems like Liposomes, Niosomes, Proniosomes, Transferosomes, Pharmacosomes, Colloidosomes, Herbosomes, Sphingosomes, Aquasomes, Ufasomes, and Electrosomes have been developed. This review includes a discussion about various lipoidal and non-lipoidal vesicular drug targeting.

Corresponding author
Ganesh Sai Myneni
GITAM Institute of Pharmacy,
GITAM Deemed to be University, Rushikonda,
Visakhapatnam, Andhra Pradesh, India – 530045.
ganeshsai011@gmail.com
9491136608

*Please cite this article in press as **Ganesh Sai Myneni** et al. Novel Vesicular Drug Delivery Systems: A Review. Indo American Journal of Pharmaceutical Research.2021:11(04).*

INTRODUCTION

NDDS aims to deliver the drug at a rate directed by the body's need during the period of treatment [1], and channel the active entity to the site of action. The biologic origin of these vesicles was first reported in 1965 by Bingham [1], and was given the name Bingham bodies [1]. Several novel vesicular drug delivery systems have been emerged encompassing various routes of administration, to achieve targeted and controlled drug delivery [1]. Targeted drug delivery is for delivering the therapeutic agent to the tissues of interest while reducing the relative concentration of the therapeutic agent in remaining tissues, improving the therapeutic efficacy, and reducing the side effects. Drug targeting is the delivery of drugs to receptors, organs, or any specific part of body to which one wishes to deliver the whole drug [2]. The targeted drug delivery system was developed by Paul Ehrlich [2], in 1909, which showed the therapeutic agent directly to diseased cells [3]. Since then, numbers of carriers were utilized to deliver the drug at target site; these include immunoglobulins, serum proteins, synthetic polymers, microspheres, liposomes [8], niosomes [63], and erythrocytes. Among different carriers, vesicular drug delivery systems are found to be well renowned [3]. These systems have also been used to improve the therapeutic index [4], solubility [3], stability and rapid degradation of drug molecules [1-4]. In this article, strive has been made to discuss various types of VDDS, emphasizing their drug targeting application [1].

Advantages [116]:

Vesicular drug delivery systems have several advantages over the conventional dosage forms and the prolonged released dosage forms [114, 115].

- Improved bioavailability
- Prolonged existence of drugs in systemic circulation.
- Sustained – release of the drug.
- It reduces the cost of therapy.
- Overcomes the difficulties of the drug insolubility, instability and rapid degradations.
- As selective uptake is taken place so reduce toxicity.
- Effective permeation of drugs into cells.
- Both the hydrophilic and lipophilic drugs can be incorporated.
- Delays elimination of rapidly metabolized drugs.

Types of Vesicular Drug Delivery System [5-6]:

a) Lipoidal biocarriers
b) Non-lipoidal biocarriers

Table 1: Types of Vesicular Drug Delivery System.

a)	Lipoidal biocarriers	b)	Non-lipoidal biocarriers
1.	Liposomes	1.	Niosomes
2.	Emulosomes	2.	Bilosomes
3.	Enzymosomes	3.	Aquasomes
4.	Sphingosomes		
5.	Ethosomes		
6.	Transferosomes		
7.	Pharmacosomes		

Lipoidal biocarriers

Liposomes:

Liposomes are superficial microscopic vesicles in which lipid bilayer structures exists with an aqueous volume completely enclosed by a membrane containing of lipid molecules. There are several components present in liposomes, with phospholipids and cholesterol being the main ingredients [1, 7-8].

Liposomes consist of concentric phospholipid bilayers that enclose an inner aqueous volume(s). For the application of drug delivery, liposomes are usually unilamellar (ULV) and they ranges in diameter from about 50 – 150 nm.

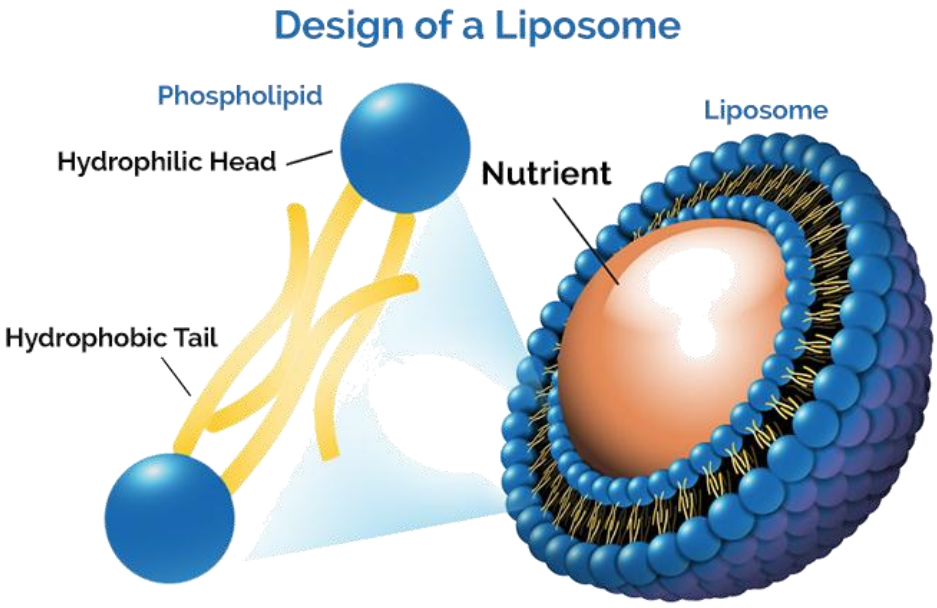

Figure 1: Liposomal Structure [10].

Advantages:

- Supplies selective passive targeting to tumor tissues [9].
- Increased efficacy and therapeutic index.
- Increased stability via encapsulation.
- Reduction in toxicity of the encapsulated agent.
- Site avoidance effect [11].
- Enhanced pharmacokinetic effects.
- It has flexibility to couple with site specific ligands to achieve active targeting.
- It is used for drug delivery systems due to its solitary structural properties.
- They can carry both the hydrophobic and hydrophobic drug. Therefore, liposomes as a drug carrier can indiscriminately deliver drugs through the cell membrane [12].
- Liposomes herbal therapy acts as carrier for small cytotoxic molecules and as a vehicle for macromolecules as a gene.
- Liposome formulation can produce sustained and controlled release of formulation and enhances the drug solubility [13].

Disadvantages:

- High production cost.
- Leakage and fusion of encapsulated drug/ molecules.
- Phospholipids undergo oxidation.
- Hydrolysis like reaction.
- Short half-life [14].

Table 2: Vesicle Types with their Size and Number of Lipid Layers [6, 15, 16].

S. No	Abbreviation	Vesicle Type	Diameter Size	No. of lipid bilayer
1.	MLV	Multilamellar Vesicles	>0.5µm	5-25
2.	OLV	Oligolamellar Vesicles	0.1 – 1µm	Approx. 5
3.	UV	Unilamellar Vesicles	All size ranges	1
4.	SUV	Small Unilamellar Vesicles	20 - 100µm	1
5.	MUV	Medium sized Unilamellar Vesicles	>100µm	1
6.	LUV	Large Unilamellar Vesicles	>100µm	1
7.	GUV	Giant Unilamellar Vesicles	>1µm	1
8.	MV	Multi vesicular Vesicle	>1µm	Multi compartmental structure

Table 3: Classification according to methods of preparation [6].

1.	Extraction method: VET (Vesicles prepared by Extraction method)
2.	French Press Cell method
3.	Fusion method
4.	IV Reverse phase Evaporation method: SUVs, MLVs & OLVs
5.	Frozen and Thawed multilayered vesicles
6.	Dehydration & rehydration method: DRV
7.	Stable Plurilamellar air vesicles method: SPLV

Table 4: Based on In-Vivo applications [6].

1.	Conventional liposomes
2.	Long circulatory liposomes
3.	Immunoliposomes
4.	Cationic liposomes
5.	Fusogenic liposomes [14]

Table 5: Several types of liposomes with composition and applications [1].

S. No.	Type	Composition	Applications
1.	Conventional Liposomes (CL)	Phospholipids with cholesterol Neutral or negatively charged[17]	Helps in targeted delivery of an anti-microbial agent to vaccination, macrophages
2.	Cationic liposomes	Positively charged cationic lipids	Helps in gene therapy [17,18]
3.	pH-sensitive liposomes	Phospholipids such as phosphat--idylethanolamine, dioleoylphos--phatidylethanolamine	Helps in tumour targeting and coated pit endocytosis
4.	Immuno-liposomes	Conventional or long circulatory liposomes with attached antibody or recognition sequence	Helps in specific targeting, Subject to receptor mediated endocytosis
5.	Magnetic liposomes	Phosphatidylcholine, cholesterol, small amounts of linear chain aldehyde and colloidal particles of magnetic iron oxide [20]	Helps in specific targeting of antibodies to brain
6.	Temperature or heat-sensitive liposomes	Dipalmitoylphosphatidyl choline	Site-specific delivery of drugs for the treatment of solid tumours
7.	Long circulatory (stealth) liposomes (LCL)	Neutral high transition tempe-rature, lipid, cholesterol and 510% of PEG [17, 19, 21]	Selective targeting to pathological areas

Preparative methods of liposomes:

All liposomes methods involve the dissolution of cholesterol, lecithin, and charge in an organic solvent which is followed by drying it to a thin film. Then dispersing film in an aqueous medium to obtain liposome suspension at a critical hydrating temperature. This method of liposome preparation includes passive loading and active or remote loading. Passive loading is which involves loading of entrapped agents before or during the manufacturing procedure. Active or remote loading is certain types of compounds with ionizable groups. Those with lipid and water solubility can be introduced into the liposomes after forming the entire vesicles.

General method of preparing liposomes involves three to four steps [6]. They are:

- Drying down lipids from organic solvent
- Dispersion of lipid in aqueous media
- Purification of resultant liposomes
- Analysis of final product

Classification modes in methods of preparation

- Physical dispersion involving handshaking and non - handshaking methods.
- Solvent dispersion includes ethanol injection, ether injection, double emulsion vesicle method, reverses phase evaporation method, and stable plurilamellar.
- Detergent solubilization.

Structural components of liposomes:

Many lipids and amphiphiles are available as liposomes raw materials or additives that are required for the formation of lipid bilayers. Phospholipids, Synthetic phospholipids, Glycerolipids, Sphingolipids, Glycosphingolipids, Steroids, Polymeric material, Charge inducing lipids [6, 14].

Phospholipids include natural and synthetic phospholipids. These natural and synthetic phospholipids are as follows

- Natural phospholipids includes Phosphotidylcholine, Phosphotidylserine, Phosphotidylethanolamine, Phosphotidylinositol
- Synthetic phospholipids includes Dioleoyl-Sn-Glycero-3-[Phospho-L-Serine (Sodium Salt)] (DOPS), Distearoylphosphotidylcholine (DSPC), Dipalmitoylphosphotidylserine (DPPS)
- Sphingolipids – Sphingomyelin
- Glycosphingolipids-Gangliosides
- Steroids – Cholesterol
- Polymeric Material – Lipids conjugate to dine, Methacrylate, Thiol group
- Charge – induced lipids - Dioctadecyldimethyl ammonium bromide/chloride (DODAB/C), Dioleoyltrimethyl ammonium propane (POTAP)
- Other substances – Stearylamine & Dicetylphosphates, Polyglycerol & polyethoxylated mono & dialkylamphiphiles

Applications of liposomes:

- Liposomes as drug delivery vehicles, controlled and sustained drug release, enhanced drug stabilization, altered pharmacokinetics and biodistribution, enzyme replacement therapy and biodistribution, enzyme replacement therapy and lysosomal storage disorders
- Liposomes in anti-microbial, anti-fungal (lung therapeutics) and anti-viral (anti HIV), Liposomal drugs, Liposomal biological response modifiers[6].
- Liposomes in tumor therapy.
  - Carrier of small cytotoxic molecules, Vehicles for macromolecules as cytokines or genes
- Liposomes in gene delivery.
  - Gene and Antisense therapy, Genetic (DNA) vaccination
- Liposomes in anti-sense oligonucleotide therapy.
- Liposomes as artificial blood surrogates
- Liposomes as radiopharmaceutical and radio diagnostic carriers
- Liposomes in cosmetics and dermatology
- Liposomes in enzyme immobilization and bioreactor technology [6].
- Immunological applications of liposomes.
  - Liposomes as an immunological (vaccines) adjuvant, Liposomal vaccines, Liposomes as a carrier of immunomodulators, Liposomes in immunodiagnostic.

Different types of liposomes that are already in the market are Doxorubicin Liposomes, Amphotericin B Liposomes, Paclitaxel Liposomes, Cytarabine Liposomes, Irinotecan Liposomes, and Cisplatin Liposomes [86].

Emulsomes:

It is a lipid based drug delivery system, especially designed for parenteral delivery of drugs having poor aqueous solubility [22]. The inner core is made up of fats and triglycerides, which are stable in form of o/w emulsion by addition of high concentrations of lecithin. They have the characteristics of both liposomes and emulsions. By virtue of solidified or semi-solidified internal oily core, it provides better opportunity to load lipophilic drugs in high concentration, at the same time a controlled release can also be expected and this also have the ability to encapsulate water soluble medicaments in aqueous compartments of surrounding phospholipids layers. The solvent-free and surfactant-free emulsomes have demonstrated high encapsulation capacity for water insoluble antifungal and anticancer drugs, showed enhanced drug delivery and improved preclinical efficacy for oral route [23]. A researcher prepared amphotericin B (an effective antifungal and anti-leishmanial agent) loaded emulsomes for the treatment of visceral leishmaniasis. This study focus on preparing macrophage (liver, spleen and bone marrow) targeted emulsomes to reduce the adverse effects of conventional treatments [24]. Raza et al prepared dithranol loaded emulsomes with enhanced biocompatibility, efficacy and stability in treatment of psoriasis [25]. Kamboj et al said, Vyas et al developed zidovudine emulsomes for sustained and targeted drug delivery to liver for the treatment of life-threatening viral infections like hepatitis, HIV and Epstein-Barr virus infection [26, 27].

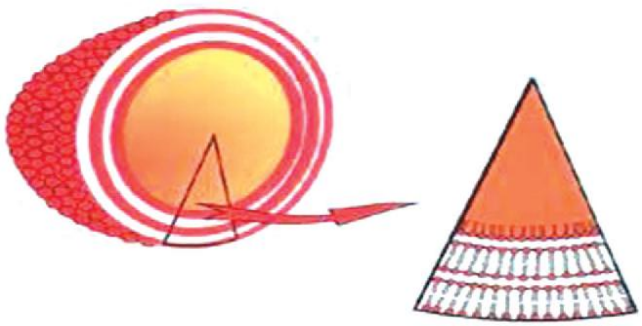

Figure 2 Emulsome Structure [41].

Preparation:

Emulsomes are prepared by mixing phospholipids and triglycerides in a weight ratio of 0.5:1. Then they are mixed at the transition temperature of 25^0C. Then the mixture is suspended to aqueous solution (>25^0C). The nano emulsion is obtained with the size of 10 – 250nm. The obtained emulsion is mixed and dissolved in volatile solvents such as dichloro methane or diethyl ether in vacuum. It forms a lipid film which is then hydrated. The resulting emulsomes can be attained at a size range of 140±15nm.

Emulsomes can be administered by the routes such as intranasal, oral, topical, parenteral and aerosol inhalation. The size range of 10 – 250nm of emulsome particle are suitable for the preparation of parenteral preparation. The nano – emulsion is administered as drops applied to the cornea or at the corners of the eye. Such eye drops are more similar to the parenteral preparation rather than topical preparation. Like parenteral preparation, preferred emulsions for installation into the eye are sterile and pH should be close to neutral or usual pH should be in the range of 6 to 8.

Composition of emulsomes: lipid core and surface active agents. Lipid core includes triglycerides [37], cholesteryl esters and cholesterol, monoesters, antioxidants, protein components [38]. Surface active agents include negatively charged lipids, phospholipids, non – natural surfactants [39].

Advantages:

- Low systemic absorption
- Site – specific and increased drug levels at injured tissues
- Reduced toxicity
- Improved pharmacological activity
- Higher loading of problematic drugs that previously could not be administered intravenously in the absence of co solvents or toxic surfactants.
- Prevents drug from harsh gastric environment as the drug is encompassed in the triglyceride lipid core (triglycerides cannot be hydrolysed by gastric pH and gastric enzymes) [28].
- Economical alternative when compared to other commercial lipid formulation as they reduce the frequency of dosing of drugs.

Disadvantages:

- Major disadvantage of standard O/W emulsion is its limited loading capacity of drug.
- Not possible to administer parenterally as it causes undesirable side effects [28].
- Higher oil content reduces the stability of the emulsion where the addition of surfactants and co-solvents are required.

Methods of preparation of emulsomes [28]

1) Lipid film formation (Hand shaking method) [29]
2) Reserve phase evaporation [32]
3) High-pressure extrusion technique [30, 31]
4) Sonication method [33]
5) Cast film method
6) Ethanol Injection method [34]
7) Detergent removal technique [35]

Emulsomes can be administered in different routes such as oral, inhalation, topical, intranasal, parenteral, aerosol. In case of parenteral preparation the particle size of emulsome should be in a range of 10 – 250nm. Nano emulsomes are used in ophthalmic preparation which is administered as drops to cornea of eye. Emulsomes for ophthalmic preparations should be sterile and the pH should be close to neutral around 6 – 8 [28, 36].

Applications of Emulsomes include incorporation of a neuroprotectant drug, Incorporation of psycho tropically active agents in emulsomes, Antifungal drugs, AIDS drugs (zidovudine), Anti – neoplastic treatment [40].

Enzymosomes:

Enzymosomes is an innovative currently emerging targeted vesicular drug delivery system. Enzymosomes fundamentally uses enzymes, which are having a targeted catalytic function for a substrate, which are incorporated within cell-like structures having high lipid background [42]. They yield newly designed liposomes, in which the enzymes are coupled covalently to the surface of lipid molecules. The liposomes so devised to provide proper micro surrounding for the enzymes to be incapacitated within them [43]. Liposomes are micro-sized vesicles consisting of a lipid bilayer enclosing with an aqueous environment. The hydrophilic drugs can be solubilised within the internal aqueous compartment and the lipophilic drugs are incorporated into the lipid bilayer membrane consisting of phospholipid-cholesterol [44]. The drug delivery systems of lipid-based are beneficial in special characteristics like lowering volume of distribution, interrupting drug clearance and alter the distribution of drug with enhanced capillary permeability towards the infected tissues and reducing toxicity associated with normal tissues, proving to give an efficient nano scale drug delivering for clinical use [45].

Sphingosomes

Sphingosomes solve the vital disadvantage of liposomes like less stability and in vivo circulation time, low tumor loading efficacy in situation of cancer therapy. They are clinically used delivery system for chemotherapeutic agent, biological macromolecule and diagnostics [46]. Due to the flexibility in size and composition, different types of sphingosomes have been developed. "Sphingosome are defined to be as concentric, bilayered vesicle in an aqueous volume which is entirely enclosed by a membranous lipid bilayer that is mainly composed of natural or synthetic sphingolipid". Liposome formulation based on sphingomyelin based cholesterol has several advantages when compared to other formulation [46]. These are much more stable to acid hydrolysis, have better drug retention characteristics. Sphingosomes are administered in many ways, include parentral route of administration such as intravenous, intramuscular, subcutaneous, and intra-arterial.

Preparation methods of sphingosomes include classical method or mechanical dispersion method and film method. Advantages of sphingosomes are increase efficacy and therapeutic index, provides selective passive targeting to tumor tissue, improve pharmacokinetic effect, increase stability, reduction in toxicity of the encapsulated agent, flexibility to couple with site specific ligands to achieve active targeting [46]. Therapeutic applications are like sphingosomes in tumor therapy and cosmetic industry. Sphingosomes may be used in gene delivery, enzyme immobilization and in immunology.

Advantages:

- Provide selective passive targeting to tumor tissue [105].
- Increase efficacy and therapeutic index.
- Increase stability via encapsulation
- Reduction in toxicity of the encapsulated agent.
- Improve pharmacokinetic effect (increase circulation time)
- Flexibility to bind with site specific ligands to achieve active targeting [105].

Ethosomes

Ethosomes are phospholipid nanovesicles used for dermal and transdermal delivery of molecules. Ethosomes have also been developed for delivering the drugs having low penetration power through skin. They are soft lipid vesicles of size range from tens of nanometers to microns, containing phospholipids, ethanol, isopropyl alcohol in relatively high concentration and water [47, 48]. Ethanol acts as penetration enhancer and fluidizes the ethosomal lipids and stratum corneum bilayer, thus allowing the soft, malleable vesicles to penetrate the disorganized lipid bilayer. The high concentration of ethanol (20-50%) is the main reason for better skin permeation ability. Ethanol confers a surface negative net charge to ethosomes due to which size of vesicles decreases. Hence, size of ethosomal vesicles increases with decrease in concentration of ethanol [49]. Ethosomes can also be used for delivery of various antifungal agents (fluconazole) antiviral agents (zidovudine, lamivudine, stavudine, and acyclovir), NSAIDS (diclofenac, aceclofenac), antibiotics (erythromycin, cannabidol) and various other drugs like ammonium glycrrhizinate, salbutamol sulfate, propranolol, testosterone, finasteride, bacitracin, and methotrexate. These have shown the enhancement of pharmacological efficacy in drug targeting to transdermal and dermal sites for the treatment of various skin diseases [27, 50 – 52].

These are some of the marketed products based on ethosomal formulation such as Cellulight EF (Hampden Health, USA) and Osmotics Lipoduction Cellulite Cream (Osmotics, Israel) [88] where the mechanism is deeper penetration into the skin, Nanominox (sinere, Germany) [89] where the mechanism is pilosebaceous, targeting and high penetration into deep layers of the skin. Noicellex (NTT, Israel) [90] where the mechanism is deeper diffusion into the skin. Supravir cream (Trima, Israel) [91] where the mechanism is lipid perturbation.

Advantages:

- Increasing efficacy and therapeutic index.
- Reduction in toxicity of the encapsulated agent.
- Improved permeation
- Suitable for large and varied groups
- Safety and non-toxicity
- Simplicity of manufacturing
- Being non-invasive
- Better stability and solubility
- Selective passive targeting

Transferosomes

Transferosome is a proprietary drug delivery technology, an artificial vesicle designed to exhibit the characteristics of a cell vesicle suitable for controlled and potentially targeted drug delivery [53]. Transferosomes are such novel vesicular drug delivery systems whose uniqueness is an ultra deformable vesicle. It can squeeze itself through a pore, many times smaller than its size owing to its elasticity, designed to enhance the skin penetration and deliver the drug non-invasively through the skin barrier without measurable loss [54, 55]. Transferosomes have been widely used as carrier for the controlled and targeted delivery of proteins, peptides, hormones and several drugs [56, 57]. The oral delivery of peptides like insulin and interferons is impossible due to their instability and rapid degradation in the harsh environment of gastro intestinal tract.

These are also difficult to diffuse through skin due to their large molecular weight, but these can be transported easily across the skin with the help of transferosomes. Romchat et. al described diractin as a medicine which contains the ketoprofen as an active substance. It was available as a gel containing 22.9 mg of ketoprofen per gram of gel. It was used to treat the symptoms of inflammation and pain associated with osteoarthritis [92].

Types of materials used in the preparation of transferosomes are phospholipids, surfactants, alcohol, buffering agent, dye [58]. Phospholipids such as soya phosphatidyl choline, Dipalmitoylphosphatidyl choline, Distearoylphosphatidyl choline is used which acts as vesicles forming component. Sodium cholate, sodiumdeoxycholate, Span – 80, Tween – 80 are the different surfactants used in preparation of transferosomes that helps in providing flexibility. Ethanol and Methanol as solvent, saline phosphate buffer (6.4) as hydrating medium and dye like Nile red or fluorescein.

As in liposomes, transferosomes also have certain limitations as they are chemically unstable due to their predisposition to oxidative degradation, lack of purity in natural phospholipids comes in the way of adoption of transferosomes as drug delivery vehicles. Their formulations are expensive.

Advantages:

- Transferosomes possess an infrastructure consisting of hydrophobic and hydrophilic moieties together [107].
- High deformability of this system gives better penetration of intact vesicles.
- They are biocompatible and biodegradable [108].
- They have high entrapment efficiency.
- Protects the encapsulated drug from metabolic degradation
- Extremely high flexibility of their membrane [109].

Pharmacosomes

They are defined as "the colloidal dispersion of drugs covalently bound to lipids that may exist as an ultrafine vesicular, micellae or hexagonal aggregates basing upon the chemical structure of drug-lipid complex." Pharmacosomes is the term obtained from pharmacon. The idea of development of vesicular pharmacosomes was on the basis of surface and bulk interaction of lipids with water [59]. Any drug having an active hydrogen atom (-COOH, -OH, $-NH_2$) can be esterified to the lipid with or without spacer chain. Synthesis of such compounds may be guided in such a way that strongly amphiphilic compound results, which will facilitate membrane, tissue or cell wall transfer in the organism. Pharmacosomes are novel VDDS having unique advantages over other drug delivery systems [60]. Pharmacosomes are amphiphilic lipoidal colloidal dispersions of drugs, covalently bound to lipids with potential to improve bioavailability of poorly water soluble and poorly lipophilic drugs [61]. TRUSOPT is one of the marketed products of pharmacosomes where it is a Sterile Ophthalmic Solution that is supplied as a sterile, isotonic, buffered, slightly viscous, aqueous solution of dorzolamide hydrochloride [93].

Advantages:

- They delivers drug at the specific site and site targeted.
- Suitable for both lipophilic and hydrophilic drugs.
- Reduce the adverse effects and toxicity
- Reduce the cost of therapy
- Improves bioavailability [110].

Non – lipoidal biocarriers

Niosomes

Niosomes are non-ionic surfactants vesicles obtained on hydration of synthetic non-ionic surfactants with or without incorporation of cholesterol or lipids [6]. Niosomes are formations of vesicles by hydrating mixture of cholesterol and non ionic surfactants. These are formed by self assembly of non - ionic surfactant in non-aqueous media as spherical, multilamellar system and polyhedral structure in addition to inverse structures which appears only in on aqueous solvent [63]. Since then a number of non - ionic surfactants have been used to prepare vesicles. e. g., Polyglycerol alkyl ethers, glucosyldialkyl ethers, crown ethers, polyoxyethylene alkyl ethers, ester linked surfactants, steroid linked surfactants, brij and a series of spans and tweens [62]. They are vesicular systems similar to liposomes that can be used as carriers of amphiphilic and lipophilic drugs. The vesicles are defined to be composed of or relating to small, sac like bodies. Niosomes and liposomes are equally active in drug delivery potential and both increase efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical stability and economy. Non-ionic surfactant vesicles are microscopic lamellar structure of size range 10-1000nm consisting of spherical, uni or multilamellar and polyhedral vesicles in aqueous media [62].

Based on the vesicle size, niosomes can be divided into three groups. These are small unilamellar vesicles (SUV, size=0.025-0.05 μm), multilamellar vesicles (MLV, size=>0.05 μm), and large unilamellar vesicles (LUV, size=>0.10 μm).

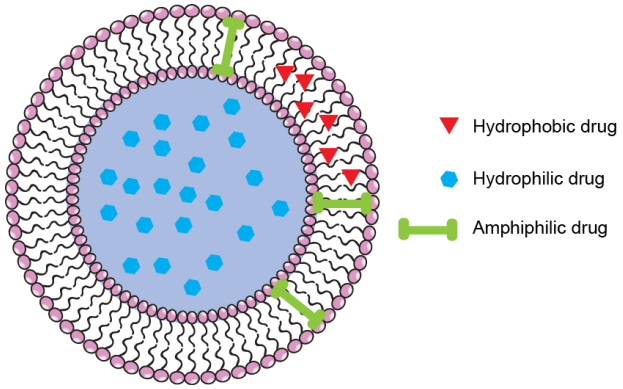

Figure 3: Niosomal structure [72].

Preparation of niosomes by using different methods on the basis of sizes of the vesicles and their distribution, entrapment efficiency of the aqueous phase & permeability of vesicle membrane and number of double layers. Preparation of small unilamellar vesicles are done by using methods like Sonication [64], Micro fluidisation [65]. Preparation of multilamellar vesicles are done by using methods like Hand shaking method [64], Trans-membrane pH gradient (inside acidic) drug uptake process [66]. Preparation of large unilamellar vesicles are done by using methods like Reverse phase evaporation technique [67], Ether injection method [64, 68]. Some other preparation methods that are involved in preparation of niosomes like multiple membrane extrusion method, niosome preparation using polyoxyethylene alkyl ether, emulsion method, lipid injection method, preparation using micelle [69].

Loreal developed and patented niosomes. But, Lancôme, the first product containing "niosome," was introduced in 1987 by Loreal. Enhanced skin penetration, stability of entrapped drugs, and better bioavailability of poorly absorbed contents make niosome an ideal choice for the cosmetics industry [94].

Characterisation of niosomes:

Shape of niosomal vesicles is supposed to be spherical and their mean diameter is determined by using laser light scattering method. Diameter can also be measured by using electron microscopy, optical microscopy, ultracentrifugation, molecular sieve chromatography; photon correlation microscopy and freeze fracture electron microscopy. Bilayer formation is measured by an X – cross formation under light polarisation microscopy [70]. Number of lamellae is measured by using nuclear magnetic spectroscopy and electron microscopy. Membrane rigidity can be measured by using fluorescence probe as a function of temperature. Entrapment efficiency is the calculation with a formula [71]:

$$\text{Entrapment efficieny (EF)} = \left(\frac{\text{Amount entrapped}}{\text{total amount}}\right) \times 100.$$

Advantages of Niosomes include Better patient compliance and better therapeutic effect in comparison to oily formulations, Can be used to deliver hydrophilic, lipophillic as well as amphiphilic drugs a can accommodate drugs with wide range of solubility, Controlled and sustained release of drugs due to depot formation. Enhance the oral bioavailability of the drugs. They are active, stable, biocompatible, nontoxic & nonimmunogenic. Protect the drug from enzymatic metabolism thud increase the stability of the drug [6].

Bilosomes

Bilosomes are a specialised novel delivery vehicle which protect vaccines from being broken down in the stomach, thereby enables the oral delivery of vaccines as an alternative to administer by IV route [73].

Mann et. al. has developed non-ionic surfactant vesicle (NISV) having liposomes like structure and stabilized them with bile salts for oral delivery of vaccines. They differ from the liposomes and niosomes in term of their composition, chemical stability and storage conditions. In order to keep away from the issues faced during GI transit, these bilosomes were formulated which not only prevented antigens from getting degraded, but also enhanced mucosal penetration [73, 75]. Vaccines that are on the basis of bilosome produced both systemic as well as mucosal immune response which was equal to immune response produced by subcutaneous route.

Composition of bilosomes is non ionic surfactant and bile salt. Bilosomes are stable chemically and in GIT. On coming to the storage and handling conditions, bilosomes do not require special conditions.

Advantages of bilosomes are they allow minor quantities of antigen to be effectual and also increase the efficacy of antigen which are weak when injected. They do not require the use of live pathogens, making them a safe and effective substitute to traditional vaccines. This non-invasive system offers advantages in user acceptance and compliance. The conventional injection method suffers from high relative costs and requires trained persons to administer the treatment [73]. They removes cold-chain requirement for preparations such as vaccine.

Some of the bilosomal formulations [95] are Cholesterol (CH)-bilosomes, Taurocholate bilosomes, Nanobilosomes with different bile salts that are used with insulin. Sodium deoxycholate nanobilosomes are used for diphtheria vaccine, hepatitis B and Baculovirus. Sodium deoxycholate microbilosomes are used for Influenza vaccine. Cholera toxin conjugated bilosomes are used for bovine serum albumin, Glucomannan – conjugated bilosomes are used for tetanus toxid.

Glycocholate bilosomes are used for calcein drug. Deoxycholate nanobilosomes are used for Cyclosporin A. Probilosomes [96] are used for Fenofibrate Salmon calcitonin. SGC and STC bilosomes are used for Tacrolimus.

Aquasomes

Aquasomes are nano particulate carrier system but instead of being simple nano particle, three layered self assembled structures, comprised of a solid phase nano crystalline core coated with oligomeric film on which biochemically active molecules are adsorbed with or without modification [75]. They are like "bodies of water" and their water like properties protect and preserve fragile biological molecules, and this property of maintaining conformational integrity as well as high degree of surface exposure is exploited in targeting of bioactive molecules like enzymes, antigens,genes, peptide and protein hormones to specific sites. These three layered structures are self-assembled by non covalent and ionic bonds [75].

Composition of Aquasomes includes ceramic and polymers that are used as core material. Albumin, gelatin or acrylate is used as polymers. Diamond particles, calcium phosphate and tin oxide are used as ceramic [78]. cellobiose, pyridoxal 5 phosphate, sucrose, trehalose, chitosan, citrate are used as coating material.

Characterization of Aquasomes

Aquasomes are characterized chiefly for their structural and morphological properties, particle size distribution, and drug loading capacity. Size distribution, structural analysis, crystallinity are used in characterization of ceramic core [76]. Carbohydrate coating, glass transition temperature are used in characterization of coated core. Characterization of drug – loaded Aquasomes includes drug payload In vitro drug release studies, In – process stability studies [77].

Applications of Aquasomes are Insulin delivery, oral delivery of acid labile enzyme, as oxygen carrier, antigen delivery, delivery of drug, delivery of gene, delivery of enzymes [75].

Some other biocarriers of VDDS

Proliposomes:

Liposomal suspension may have shelf life limited and to overcome the stability issues associated with this liposomes, a new "pro-liposomes" method is developed that can produce liposomes quickly when there is a need and without excessive manipulation [97]. Pro-liposomes (PLs) were discovered [98] in 1986. They are free-flowing granular products and dry. On hydration or on contact with biological fluids in the body they are formed in to liposomal dispersions. They are containing water soluble porous powder and phospholipid [99]. For the production of commercial liposome products, Pro-liposome is the most widely used and cost-effective method. As they are accessible in dry powder form, they were easy to distribute, transfer, measure and store, making it a diverse system. Solubility and bioavailability issues of many drugs can be overcome by developing pro-liposomal formulations [100]. Methods of Preparation of proliposomes are Film deposition on carrier method [101], Spray drying method [97], Fluidized bed method [99], Supercritical anti – solvent method [100]. Evaluation tests of proliposomes are Scanning electron microscopy, transmission electron microscopy, hydration study, zeta potential, Flow property. Proliposomes can be formulated on the basis of routes of administration like parenteral, oral, pulmonary, mucosal, transdermal, ocular drug deliveries and as pressurized metered dose inhalers (pMDI), Dry powder inhalers (DPIs) & Nebulizers [97].

Advantages:

- Increase the dissolution of a poorly soluble drug
- Increase lipophilicity
- Improves permeability
- Improve intestinal uptake
- Decrease hepatic first-pass metabolism
- Improve gastric/intestinal stability of the encapsulated drug.
- Ease of translating into a desired dosage form

Proniosomes:

Proniosomes are dehydrated preparations employing suitable non-ionic surfactants and carrier, the preparation further yields niosomes on hydration with water. Proniosomes are present in transparent, translucent or semisolid gel structure because of limited solvent presence and these are mixture of liquid crystals like lamellar, hexagonal, and cubic. The suitability of drug for the formulation of proniosomes are it should have low aqueous solubility drugs, high dosage frequency drugs, drugs with lower half-life, controlled drug delivery suitable drugs. Preparation methods of proniosomes are slurry method, coacervation phase separation method, spray coated method [103]. Formation of Niosomes from Proniosomes by hydration as the niosomes are prepared from the proniosomes by adding the aqueous phase with drug to the proniosomes with brief agitation at 80^0C for 2 minutes to get niosomal suspension. It provides rapid reconstitution of niosomes with minimal residual carrier. Methods used for in-vitro drug release from proniosomal vesicles are Franz diffusion cell, Dialysis tubing, Reverse dialysis [104]. Proniosomes are characterized by angle of repose my using funnel, Scanning Electron microscopy (SEM) for the particle size, Optical microscopy, Vesicle Size measurement and entrapment efficiency. Applications of proniosomes include Drug targeting, Anti-neoplastic treatment, Leishmaniasis, Delivery of Peptide Drugs [103].

Advantages:

- Physically stable compared to niosomes [104].
- Uniform in size [103].
- No requirement of special conditions for storage [111].
- Easy in handling, storing, transport and distribution [111].

Probilosomes:

Probilosome vesicular drug delivery systems were developed to avoid acid degradation of the drug and to enhance its oral bioavailability by resisting the drug release in acidic pH of the stomach [96]. Probilosomes are free-flowing, dry powder formulations consisting of lipids or surfactants, drug and carriers like mannitol, maltodextrin. Upon hydration, disperse to form bilosomal vesicles. They can also overcome the issues related to physical stability as they are easy to store, transport, distribute and administer [96]. Lakshmi PK. et al has described that Rosuvastatin calcium was an anti-hypertensive drug which belongs to BCS class II, selected as a model drug, having acid degradation in the stomach and low oral bioavailability (less than 20 %) [96].

Cryptosomes:

Cryptosomes, a novel emerging vesicular drug delivery system which can overcome the disadvantages associated with conventional drug delivery systems like high stability, increased bioavailability, sustained release, decreased elimination of rapidly metabolizable drugs [80]. Cryptosome is a lipid vesicle that circulates in blood for long period of time after systemic applications and has decreased phagocyte mononuclear uptake [80]. Lipid vesicles with a surface coat composed of phosphatidylcholine and of suitable polyoxyethylene that are derived from phosphatidyl ethanolamine, capable of ligand mediated drug targeting [6, 81].

Discosomes:

Discosomes are the modified forms of niosomes that may also act as carriers of ophthalmic drugs [82]. The size of discosomes differs from 12 to 16µm. They get solubilised with non-ionic surfactant solutions. They show ligand mediated drug delivery [6].

Genosomes:

Genosome is a DNA and lipid complex which helps to deliver genes. They can be a form of non – viral gene therapy as complex doesn't require any components of virus to transport genetic material [79]. Artificial macromolecular complexes for functional gene transfer. Cationic lipids are most suitable as they possess high biodegradability and stability in the blood stream.

Photosomes:

Photosome is formed of Photolysases encapsulated in liposomes, which release the content photo triggered charges in membrane permeability characteristics. Its pH level ranges from 7.0 to 8.0 [83]. Applications of phytosomes include Silymarin Phytosome, Phytosomes of grape seed, phytosome of green tea, phytosome of curcumin.

Advantages:

- Enhance the bioavailability.
- Enhance percutaneous absorption.
- Hepatoprotective effect.
- Appropriate delivery of drug to the respective tissues.
- No problem in drug entrapment while formulating phytosomes.

Virosomes:

Virosomes are the vehicles with spherical shape having phospholipid mono/bilayer membrane. Different types of glycoproteins can be present on the surface of virosome. Central cavity of virosome holds therapeutic molecules like nucleic acids, proteins and drugs [84].

Advantages:

- Virosomes are biodegradable, biocompatible and non-toxic
- No chances of auto-immunogenity or anaphylaxis [112].
- Efficient in delivering the drug into cytoplasm of target cell.
- Provides protection to drugs from degradation.
- Promotes fusion activity in the endolysosomal pathway [113].

Proteosomes:

They are very large protein complexes, known as multi – subunit enzyme complex and present in the cytosol to degrade unneeded or damaged proteins by proteolysis [85]. They regulate a wide range of cellular processes.

CONCLUSION

Vesicular systems have been noticed as substantially useful carrier systems in many scientific domains. Over the decades, vesicular system was being investigated as a major important drug delivery system because of their flexibility to be tailored for varied desirable purposes. Due to the site-specific targeting of drugs and lots of other advantages, VDDS is gaining popularity in current situation. Drugs can be comfortably and directly targeted to their site of action to avoid toxicity and undesired effects to other sites, additionally these can be used for the enhancement of bioavailability, to reduce the dose of the drug administered and to enhance the therapeutic action of drug. VDDS is beneficial for drugs having narrow therapeutic index as targeting of drug to their site of action improves the overall PKPD profile of drug and hence improvement in the overall therapy of the disease.

ACKNOWLEDGEMENT

The authors are grateful to GITAM Institute of Pharmacy, GITAM (Deemed to be University) for providing necessary facilities and support.

Declaration of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. Biju SS, Talegaonkar S, Mishra PR, Khar RK; Vesicular systems: An overview; Indian J Pharm Sci.; 2006; 68(2); 141-153.
2. Manish G, Vimukta S; Targeted drug delivery system: A Review; Res J Chem Sci.; 2011; 1(2); 135-138.
3. Mujoriya R, Bodla RB, Dhamande K, Singh D, Patle L.; Niosomal drug delivery system: the magic bullet; J Appl Pharm Sci. 2011; 01(09); 20-23.
4. Kumar R, Kumar S, Jha SS, Jha AK. Vesicular system-carrier for drug delivery. Der Pharmacia Sinica. 2011; 2(4); 192-202.
5. R, B.D.S., Topics in Pharmaceutical Sciences. Vol. 57. 1985: Elsevier Science Publisher, New York USA.
6. B. Narasimha Rao, K. Ravindra Reddy, B. Mounika, S. Rahath Fathima, A. Tejaswini; Vesicular Drug Delivery System: A Review; International Journal of ChemTech Research, 2019, 12(5): 39-53.
7. Jain NK. Advances in Controlled and Novel Drug Delivery. CBS Publishers, New Delhi, India (2003) 273-278.
8. Namdeo G. Shinde*, Nagesh H. Aloorkar, Ajit S. Kulkarni.; Recent advances in Vesicular drug delivery system; Research Journal of Pharmaceutical Dosage Forms and Technology; 2014; 110-120.
9. Nikalje AP, Tiwari S. Ethosomes: a novel tool for transdermal drug delivery. Int J Res Pharm Sci. 2012; 2(1): 1-2.
10. http://www.integratedhealth.com/supplements/liposomes.html (accessed on 03-11-2020)
11. Gill V, Kumar MS, Khorana B, Arora D, Mahadevan N. Development of amphotericin B loaded modified emulosomes for visceral leishmaniasis: in vitro. Int J Recent Adv Pharm Res 2011; 2: 14-20.
12. V. H. K. Li, J.R.R., V. H. L. Lee; Marcel Dekker Inc, NY, Controlled Drug Delivery: Fundamentals & Applications. 1987.
13. Talegaonkar, S., Vesicular systems: An overview. Indian Journal of Pharmaceutical Sciences, 2006. 68(2): p. 141.
14. SaurabhBansal, Chandan Prasad K., Geeta Aggarwal, SL Harikumar., A Comparitive Review on Vesicular drug delivery system and Stability issues. International Journal of Research in Pharmacy and Chemistry 2013, 2(3). 10
15. Abdus Samad., Y. Sultana., M. Aqil. 2007. Liposomal drug delivery systems: an update review. Current Drug Delivery. 4: 297-305.
16. Pawar Vinita, Mishra Kumar Shiv, Yadav Mahavir, Tiwari Archana; Liposome: A Powerful Approach Festinates Drug Delivery System; International Journal of Drug Delivery Technology; 2013; 3(1); 4-7
17. Storm G, Crommelin DJA. Liposomes: quo vadis. Pharm Sci Technol Today. 1988; 1(1):19-31.
18. Samad A, Sultana Y, Aqil M. Liposomal systems: an update review. Curr Drug Deliv.2007; 4:297-305
19. Wagner A, Uhl KV. Liposome technology for industrial purposes; .J Drug Deliv. 2011; 2011:1-9.
20. Kelly C, Jefferies C, Cryan SA. Targeted liposomal drug delivery to monocytes and macrophages; .J Drug Deliv. 2011; 2011:1-11.
21. Shao P, Wang B, Wang Y, Li J, Zhang Y. The application of thermo sensitive nano carriers in controlled drug delivery. J Nanomater. 2011; 2011:1-12.
22. Bhatt DA, Pethe AM. Lipoidal technology-a promising drug delivery for poorly water soluble drugs.Int J Pharm Res Dev. 2010; 2(7):1-11.
23. Kumar D, Sharma D, Singh G, Singh M, Rathore MS. Lipoidal soft hybrid biocarriers of supra molecular construction for drug delivery. Int. Scholar Res Network Pharm. 2012; 2012:1-14
24. Gill V, Kumar MS, Khurana B, Arora D, Mahadevan N. Development of amphotericin B loaded modified emulsomes for visceral leishmaniasis: in vitro. Int J Recent Adv Pharm Res2011; 2:14-20.
25. Raza K, Katare OP, Setia A, Bhatia A, Singh B. Improved therapeutic performance of dithranol against psoriasis employing systematically optimized nanoemulsomes; J Microencapsul. 2012:1-12.
26. SP, Subhedar R, Jain S. Development and characterization of emulsomes for sustained and targeted delivery of an antiviral agent to liver. J Pharm Pharmacol.2006; 58:321-326.
27. Sunil Kamboj*, Vipin Saini, Nancy Magon, Suman Bala, Vikas Jhawat; Vesicular drug delivery systems: A novel approach for drug targeting; International Journal of Drug Delivery 5 (2013) 121-130.
28. Aswathy S Nair ,Vidhya K.M, Saranya T, Sreelakshmy K, Sreeja C Nair; emulsomes: a novel liposomal formulation for sustained drug delivery; Int. Res J Pharm. App Sci., 2013; 3(5):192-196.

29. Dipali S R, Kulkarni S B, Betageri GV. Comparative study of separation of non-encapsulated drug from unilamellar liposomes by various methods. Journal Pharm Pharmacol, 1996; Nov; 48 (11); 1112 – 5.
30. Batzri S, Korn ED. Single bilayer liposomes prepared without sonication. Biochem Biophys Acta, 1973; 298: 1015-9.
31. Ko T, Bickel U. Reverse phase evaporation. AAPS Pharmaceutical Science Technology. 2012; 13(2): 373-378.
32. Singh S K,Rajera R, Nagpal K, Mishra DN. Niosomes: A controlled and novel drug delivery system. Bio Pharm Bull, 2011; 34: 945-53.
33. Vyas S P, Gupta S, Dube A; Antileismianial efficacy of Ampotericin B bearing emulsomes against experimental visceral leishmaniases; Journal Drug Targeting, 2007; 15: 437-444.
34. Vyas S P, Gupta S, Dube A. Development and Characterization of amphotericin B bearing emulsomes for passive and active macrophage targeting; Journal Drug targeting, 2006; 15: 206-217.
35. Nerurkar M M, Burton P S, Borcardt R T; The use of surfactants to enhance the permeability of peptides through Caco-2-cells by inhibition of an apically polarized efflux system; Pharmacy Research; 1996; 3: 528-534.
36. Ziv E, Bendayan M. Intestinal absorption of peptides through the enterocytes. Micro science Research Technology, 2000; 49: 346-52.
37. Humberstone AJ, Carman WN. Lipid-based vesicles for the oral delivery of poorly water soluble drugs. Advanced Drug Delivery Review, 1997; 25: 103-128.
38. Shreier H, Bouwstra J .Liposomes and niosomes as topical drug carriers: Dermal and Transdermal drug delivery. Journal Control Release, 1994; 30: 1-15.
39. Brocks DR, Betageri G V.; Enhanced oral absorption of halofantrine enantiomers after encapsulation in a proliposomal formulation; Journal Pharm Pharmacol, 2002; 54; 1049-1053.
40. Ljeoma F U, Vyas S P. Non-ionic surfactant based vesicles in drug delivery. International Journal Pharmaceutical science, 1998; 12: 33-70.
41. R. Kumar, Nirmala Seth, S. Kumar; Emulsomes: An emerging vesicular drug delivery system; Journal of Drug Delivery & Therapeutics; 2013, 3(6); 133 – 142.
42. Shefrin S., Sreelaxmi C. S., Vishnu Vijayan, Sreeja C. Nair; Enzymosomes: A rising effectual tool for targeted drug delivery system; International Journal of Applied Pharmaceutics; 9 (6); 2017; 1 – 9.
43. Akbarzadeh A, Sadabady RR, Davaran S. Liposome: classification, preparation and applications. Nanoscale Res Lett 2013; 8; 102-11.
44. Sharma S, Mishra L, Grover I, Gupta A Kaur. Liposome: vesicular system an overview. Int J Pharm Pharm Sci.; 2010; 2.
45. Zylberberg C, Matosevic S. Pharmaceutical liposomal drug delivery: a review of new delivery systems and look at the regulatory landscape. Drug Delivery 2016; 23; 3319 - 29.
46. Seema M. Jadhav, Pournima Morey, Mrs. Manisha Karpe, Vilasrao Kadam; novel vesicular system: an overview; Journal of Applied Pharmaceutical Science 02 (01); 2012: 193-202.
47. Gaspar MM, Martins MB, Corvo ML, Cruz MEM. Design and characterization of enzymosomes with surface-exposed superoxide dismutase. Bio chimica Bio physica Acta. 2003; 1609:211-217.
48. Vijayakumar MR, Sathalia AH, Arun K. Formulation and evaluation of diclofenac potassium ethosomes. Int J Pharm Pharm Sci. 2010; 2(4):82-86.
49. Nikalje AP, Tiwari S. Ethosomes: a novel tool for transdermal drug delivery. Int J Res Pharm Sci. 2012; 2(1):1-20.
50. Bhalaria MK, Naik S, Misra AN. Ethosomes: a novel delivery system for antifungal drugs in the treatment of topical fungal diseases. Indian J Exp Biol. 2009; 47:368-375.
51. Jain S, Tiwary AK, Sapra B, Jain NK. Formulation and evaluation of ethosomes for transdermal delivery of lamivudine. AAPS Pharm Sci Tech. 2007; 8(4):E1-E9.
52. Presa PDL, Rueda T, Morales MDP, Chichon JF, Arranz R, Valpuesta JM, Hernando A. Gold nanoparticles generated in ethosome bilayers as revealed by cryo-electron-tomography. J PhyChem B. 2009; 113:1-30.
53. https://en.wikipedia.org/wiki/Transfersome (accessed on 05-11-2020)
54. Malakar J, Gangopadhyay A, Nayak AK. Transferosome: an opportunistic carrier for transdermal drug delivery system. Int Res J Pharm. 2012; 3(3):35-38.
55. Ambarish G, Prajapati SK, Anand JP, Akhtar A, Aviral. Ultradeformable vesicle as a novel drug delivery system.Int Res J Pharm. 2012; 3(8):116-120.
56. Kaushik A, Dwivedi A, Sunda M. Transferosome: the drug loaded ultradeformable vesicles for transdermal drug delivery. Int Res J Pharm. 2011; 2(11):40-42.
57. Prajapati ST, Patel CG, Patel CN. Transferosomes: a vesicular carrier system for transdermal drug delivery. Asian J Biochem Pharm Res. 2011; 1(2):507-524.
58. Kaushik A, Dwivedi A, Sunda M. Transferosome: the drug loaded ultradeformable vesicles for transdermal drug delivery. Int Res J Pharm. 2011; 2(11):40-42.
59. P. H. Sharma, P. V. Powar, S. S. Sharma; Pharmacosomes: A novel drug delivery system; The Pharma Innovation Journal 2014; 3(10): 94-100.
60. Patel JL, Bharadia PD. A review on: pharmacosomes as a novel vesicular drug delivery system. World J Pharm Res. 2012; 1(3):456-469.
61. Semalty A, Semalty M, Singh D, Rawat MSM. Development and physicochemical evaluation of pharmacosomes of diclofenac.Acta Pharm. 2009; 59:335-344.

62. E. Touitou. Ethosomes- novel vesicular carriers for enhanced delivery: Characterization and skin penetration properties. Journal of Controlled Release, 65 2000: 403-418.
63. Jadhav SM, MoreyP, Karpe M, Kadam V., Novel Vesicular System: an overview. J. Appli. Sci. 2012; 2(1): 193-202.
64. Baillie AJ, Coombs GH, Dolan TF, Laurie J. Non-ionic surfactant vesicles, niosomes, as delivery system for the anti-leishmanial drug, sodium stibogluconate. J Pharm Pharmacol. 1986; 38:502–5.
65. Khandare JN, Madhavi G, Tamhankar BM. Niosomes novel drug delivery system. East Pharmacist. 1994; 37:61–4.
66. Mayer LD, Bally MB, Hope MJ, Cullis PR; Uptake of antineoplastic agents into large unilamellar vesicles in response to a membrane potential; Biochim Biophys Acta. 1985 Jun 27; 816(2):294-302.
67. Naresh RA, Chandrashekhar G, Pillai GK, Udupa N. Antiinflammatory activity of Niosome encapsulated diclofenac sodium with Tween-85 in Arthitic rats. Ind J Pharmacol. 1994; 26:46–8.
68. Rogerson A, Cummings J, Willmott N, Florence AT; The distribution of doxorubicin in mice following administration in niosomes. J Pharm Pharmacol. 1988; 40:337–42.
69. Karim Masud Kazi, Asim Sattwa Mandal, Nikhil Biswas, Arijit Guha, Sugata Chatterjee, Mamata Behera, Ketousetuo Kuotsu; Niosome: A future of targeted drug delivery systems; J Adv Pharm Technol Res; 2010, 1(4); 374 – 380.
70. Manosroi A, Wongtrakul P, Manosroi J, Sakai H, Sugawara F, Yuasa M, et al. Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. Colloids Surf B. 2003; 30:129–38.
71. Balasubramaniam A, Kumar VA, Pillai KS; Formulation and in vivo evaluation of niosome-encapsulated daunorubicin hydrochloride; Drug Dev Ind Pharm. 2002 Nov; 28(10):1181-93.
72. Saraswathi T. S, Mothilal M., Jaganathan M. K.; Niosomes as an emerging formulation tool for drug delivery – A review; Int J App Pharm, Vol 11, Issue 2, 2019, 7-15
73. Chilkwar RN, Nanjwade BK, Nwaji MS, Idris SM, Mohamied AS. Bilosomes Based Drug Delivery System. J Chem Applications. 2015; 2(1): 5.
74. Mann JF, Ferro VA, Mullen AB, Tetley L, Mullen M, et al. (2004) Optimisation of a lipid based oral delivery system containing A/Panama influenza haemagglutinin. Vaccine 22: 2425-2429.
75. Sanjay S. Jain, Pramod S. Jagtap, Neha M. Dand, Kisan R. Jadhav and Vilasrao J. Kadam; aquasomes: A novel drug carrier; Journal of Applied Pharmaceutical Science 02 (01); 2012: 184-192.
76. Vyas S.P., Goyal A.K., Khatri K., Mishra N., Mehta A., Vaidya, B., et al. Aquasomes—a nanoparticulate approach for the delivery of antigen. Drug Dev Ind Pharm. 2008; 34:1297-1305.
77. Vyas S.P., Goyal A.K., Rawat A., Mahor S., Gupta P.N., Khatri K. Nanodecoy system: a novel approach to design hepatitis B vaccine for immunopotentiation. Int J Pharm. 2006; 309:227-233.
78. Rawat M., Singh D., Saraf S., Saraf S. Development and in vitro evaluation of alginate gel-encapsulated, chitosan-coated ceramic nanocores for oral delivery of enzyme. Drug Dev Ind Pharm. 2008; 34:181-188.
79. https://en.wikipedia.org/wiki/Genosome. (accessed on 05-11-2020)
80. Aiswarya M. U., Keerthana raju, Revathy B. Menon, Lakshmi V. S., Sreeja C, Nair; Cryptosomes: A revolutionary breakthrough in novel drug delivery; Int J App Pharm, Vol 11, Issue 1, 2019, 7-13.
81. Immordino ML, Dosio F, Cattel L. Stealth liposomes: review of the basic science, rationale, and clinical applications, existing and potential. Int J Nanomed 2006; 1:297–315.
82. PrzemysBaw Baranowski, Bohena Karolewicz, Maciej Gajda, and Janusz Pluta; Ophthalmic Drug Dosage Forms: Characterisation and Research Methods; Hindawi Publishing Corporation 2014.
83. http://dir.cosmeticsandtoiletries.com/detail/tradeName.html?id=17127 (accessed on 03-11-2020)
84. https://en.wikipedia.org/wiki/Virosome (accessed on 05-11-2020)
85. Sharif M Shaheen; Proteosomes and Immunoproteosomes in vaccine platform; Int J Pharm Sci & Scient Res.; 2(6); 2016, 234 – 236.
86. Global Market Study on Liposomes: Significant Adoption of Liposomes being Witnessed to Enhance Drug Delivery; persistencemarketresearch.com (accessed on 30-12-2020)
87. Nanomedicine and Drug Delivery; Taylor & Francis Group; 2012 by Apple Academic Press, Inc. Vol – 1.
88. Stefanie Luebberding, Nils Krueger &Neil S. Sadick; Cellulite: An Evidence-Based Review; American Journal of Clinical Dermatology; 16(4); May 2015.
89. Ibrahim M Abdulbaqi, Yusrida Darwis, Nurzalina Abdul Karim Khan, Reem Abou Assi, and Arshad A Khan; Ethosomal nanocarriers: the impact of constituents and formulation techniques on ethosomal properties, in vivo studies, and clinical trials; Int J Nanomedicine. 2016; 11: 2279–2304.
90. Kumar L, Verma S, Singh K, Prasad DN, Jain AK; Ethanol Based Vesicular Carriers in Transdermal Drug Delivery: Nanoethosomes and Transethosomes in Focus. NanoWorld J 2016; 2(3): 41-51.
91. Touitou & Godin; Dermal drug delivery with ethosomes: therapeutic potential; Future Medicine Ltd; 4(4), 465–472; 2007.
92. Shakthi Apsara Thejani Opatha, Varin Titapiwatanakun and Romchat Chutoprapat; Transfersomes: A Promising Nanoencapsulation Technique for Transdermal Drug Delivery; Pharmaceutics – mdpi; 2020, 12, 855.
93. www.accessdata.fda.gov/drugsatfda_docs/label/2010/020408s047lbl; (accessed on 31-12-2020).
94. Thakur Gurjeet Singh, Neha Sharma, Nanobiomaterials in Galenic Formulations and Cosmetics; Applications of Nanobiomaterials Volume 10; 2016; 149 – 174.
95. Elnaggar Y; Multifaceted applications of bile salts in pharmacy: an emphasis on nanomedicine; International Journal of Nanomedicine; 2015; 10(1)3955—71

96. Haritha P, Lakshmi PK; Probilosomes: A Novel Bile Salt Containing Nanocarrier for Enhancing Oral Bioavailability; International Journal of Pharmaceutical Investigation; 2020; 10(1).
97. Muneer S, Masood Z, Butt S, Anjum S, Zainab H, Anwar N, Ahmad N; Proliposomes as Pharmaceutical Drug Delivery System: A Brief Review; J Nanomed & Nanotechnol 2017, 8(3).
98. Payne NI, Timmins P, Ambrose CV, Ward MD, Ridgway F (1986) Proliposomes: a novel solution to an old problem. J pha sc 75: 325-329.
99. Manjula D, Shabaraya AR, Shyale S (2014) Topical Delivery of Fenoprofen Proliposomes: Preparation, Evaluation and In Vitro Release. Int J Pha Sc In 3: 06-12.
100. Ashok K, Jukanti R (2012) Euro J Phar Bio, pp: 347-357.
101. Janga KY, Jukanti R, Velpula A, Sunkavalli S, Bandari S, et al. (2012) Bioavailability enhancement of zaleplon via proliposomes: Role of surface charge. Euro J Phar Biop 80: 347-357.
102. G. V. Radha, K. Trideva Sastri, P. Prathyusha, P. Bhanu, Jampala Rajkumar; Formulation and Evaluation of Aceclofenac Proniosome loaded orabase for management of dental pain; Int J App Pharm, 10(6), 2018, 204-210.
103. Indira U and Uma Shankar M.S: Proniosomes as a Drug Carrier: A Review. Int J Pharm Sci Res. 3(12); 4617-25.
104. Alsarra A, Bosela AA, Ahmed SM and Mahrous GM. Proniosomes as a drug carrier for transdermal delivery of ketorolac. Eur J Pharm and Biopharm. 2004: 105; 1-6.
105. Ashok K, Rajendra Kumar A, Sreekanth Nama; Sphingosomes:: Vesicular Drug Delivery System; IJPRBS, 2013; Volume 2(2): 305-312.
106. Hamideh Razavi, Sajjad Janfaza; Ethosome: A nanocarrier for transdermal drug delivery; Journal of Paramedical Sciences, 2015; Vol-6(2); 38 – 43.
107. Kumar R, Singh M, Bala R. Seth N, Rana A; Transferosomes: A novel approach for transdermal drug delivery; International research journal of pharmacy, 2012; 3(1).
108. Patel SN; A vesicular transdermal delivery system for enhance drug permeation-ethosomes and transferosomes; International Pharmaceutical Sciencia, 2012; 2(2).
109. Solanki et al.; Transferosomes-A Review; World journal of pharmacy and pharmaceutical sciences; Vol 5(10); 435 – 449.
110. Bommala Supraja, Saritha Mullangi; An updated review on pharmacosomes, a vesicular drug delivery system; Journal of drug delivery and therapeutics. 2019; 9(1-s); 392-402.
111. Dibyalochan Mohanty et al; Proniosome: A novel trends in Pharmaceutical sciences; J. Global Trends Pharm Sci, 2018; 9(1): 5083 – 5095
112. Gluck R. Mischler R, Finkel B. Que JU, Scarpa B, Crryz SJ; Immunogenicity of new virosome influenza vaccine in elderly people. Lancet 1994; 344; 160 – 3.
113. Priyanka Rathore, Gaurav Swami; Virosomes: A novel Vaccination Technology; IJPSR; 2012; 3(10); 3591-3597.
114. Talegaonkar, S., et al., Vesicular systems: An overview. Indian Journal of Pharmaceutical Sciences, 2006. 68(2): p. 141.
115. Todd, J.A., Modest, E. J., Rossow, P. W. and Tokes, Z. A., Biochem. Pharmacol. Vol. 34. 1982. 541.