

An Overview on NanoNiosomes: As an Optimistic Drug Delivery System in Targeted Drug Delivery

ABSTRACT

Targeted drug-delivery systems are used for the administration of pharmaceutical medicament enables the localization of drugs to diseased sites. Different types of drug-delivery systems uses carriers, like immunoglobulins, serum proteins, synthetic polymers, liposomes, nanoparticle and microspheres. Niosomes are an emerging type of novel vesicular systems. Now they are being fervent explored as potential carriers for targeted drug delivery. In addition to conventional, oral, and parenteral routes, they are liable to be delivered by ocular, transdermal, vaginal, and inhalation routes. Nano-niosomes are non-ionic surfactants based vesicles that are biodegradable, relatively nontoxic, more stable and inexpensive than liposomes. Other component, such as cholesterol, can be used to give the rigidity to the niosomes structure. The unique vesicular structure of niosomes, with their bilayer lamellae assembled by nonionic surfactants, is able to increase the bioavailability of a drug to a predetermined area for a period. The amphiphilic nature of niosomes promotes their efficiency in encapsulating hydrophobic or hydrophilic drugs. These nonionic vesicular carriers not only transport the pharmacological agents to target site or disease site, avoiding normal tissues and reducing toxicity in the rest of the body, but also protect drugs from degradation, increase the half-life, payload and solubility of drug and reduce renal clearance. This present review describe overview of niosomes formulation aspects, structure, types of niosomes, advantages, and disadvantages, method of preparation as well as some general observations on niosomes.

Keywords: *NanoNiosomes, Nonionic surfactant, Targeted drug delivery system*

1. INTRODUCTION

In recent year targeted drug delivery system has been much more attention in delivery of drug at targeted site. The aim of targeted drug delivery system is that to concentrate the drug in the tissues of interest while decreasing the relative concentration of the drug in the remaining tissues. As a result, drug is localized on the targeted site. Thus, surrounding tissues are not affected by the drug. Nanocarrier is a great approach for the delivery of drug molecule to the target sites. Liposomes, immunoglobulin, synthetic polymers, niosomes and microspheres have all been used as carrier for targeting of drug [1].

Niosomes is vesicles which have lamellar (bilayer) structures that are built by a mixture of a non-ionic surfactant and cholesterol that can increase the rigidity of the bilayer. Niosomes are nonionic surfactant vesicular Nanocarrier that have received a much of attention because of their unique properties. Niosomes are considered an alternative to other vehicular carrier, specifically liposomes, due to their unique properties such as simple preparation, low cost, high stability, and simultaneous encapsulation of hydrophobic and hydrophilic drugs [2].

Thus Niosomes have unique properties as compared to liposomes. Niosomes vesicles are colloidal particles they have amphiphilic molecules surrounds an aqueous compartment. Composed of both hydrophilic (heads) and hydrophobic (tails) classes and are self-assembling, aggregating into a variety of shapes like micelles or into a planar lamellar bilayer. In the bilayer structure, hydrophobic parts are rejected from the aqueous solvent, while the hydrophilic heads remain in contact with the aqueous solvent. By changing the composition of the vesicles, size, lamellarity, tapped volume, surface charge and concentration the properties of the vesicles can be changed [2, 3].

The different forces such vanderwals force among the surfactant molecules, repulsive forces arising from electrostatic interactions between the charged groups of surfactant molecules, entropic repulsive forces of the head groups of surfactants, short-acting repulsive forces, etc. acts within the vesicles. These all forces are responsible to hold the vesicular structure of niosomes in place. However, the class of surfactant, temperature, detergents, membrane spanning lipids (cholesterol), in situ interfacial polymerization of surfactant monomers, and the presence of a charged molecule all affect the stability of niosomes [4].

2. STRUCTURAL COMPONENTS OF NIOSOMES

2.1. Niosomes Structure and Components

Niosomes are spherical in shape and consist of microscopic lamellar such as unilamellar or multilamellar structures. Because of their unique bilayer vesicular structure niosomes can encapsulate both hydrophilic and lipophilic drugs [5]. Lipophilic drugs are entrapped by partitioning into the lipophilic domain of the bilayers, while hydrophilic drugs are adsorbed on the bilayer surfaces. The bilayered vesicular structure is an self-assembly of hydrophobic tail portion of surfactant monomers which is shielded away from the aqueous space located at the center and hydrophilic groups in contact with the same [6, 7].

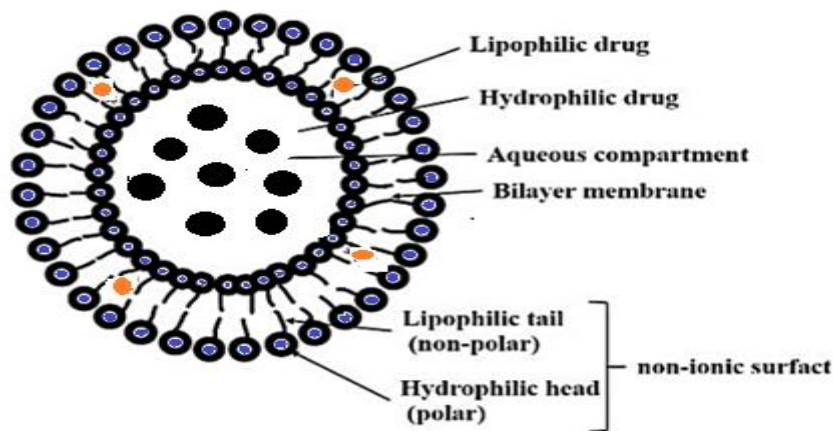


Fig: 01 Structure of niosome [4, 5]

The three major components are required for the preparation of niosomes such as: lipid compounds (cholesterol), nonionic surfactants and hydration medium.

2.2. Nonionic Surfactant

Many synthetic amphiphiles can form vesicles, but as most of them are ionic and toxic, they are generally not suitable for the use of drug carriers. Niosomes are multilamellar vesicles prepared from synthetic nonionic surfactants [8]. Nonionic surfactant used in formulation of niosomes as they carry no charge. As compared to anionic, amphoteric or cationic, nonionic surfactants are less toxic, less hemolytic, producing less irritating to cellular surfaces, they are more stable and biocompatible. As a result, they are favored for the in vitro and in vivo development of stable niosomes. They have different functions such as acting as solubilizers, wetting agents, emulsifiers and permeability enhancers. Nonionic surfactant is P-glycoprotein inhibitor; this property is responsible for enhancing the drug absorption and targeting drug to specific tissues. The major nonionic surfactant amphiphiles used in the niosomes formulation are alkyl ether, alkyl esters, alkyl amides and ester of fatty acids. The hydrophilic-lipophilic balance (HLB) and critical packing parameter (CPP) are crucial in the selection of surfactant molecules for the formulation of niosomes. The term HLB is used to indicate balance between hydrophilic-lipophilic substances [9, 10]

2.2.1. Hydrophilic-Lipophilic Balance

In pharmaceutical research, HLB is a dimensionless parameter is used to measure the solubility of surfactant molecules. The lower HLB value indicate to more lipophilic surfactant and the higher HLB indicate to more hydrophilic surfactant. Those surfactant having HLB value range between 14-17 is not suitable for forming the bilayer structure of niosomes because the HLB value of surfactant increases, increase alkyl chain thereby, the size of niosomes increases. It has been found that surfactants with an HLB value range between 4 to 8 can be form niosomes, while surfactants with an HLB value of 6 or higher require the optimum concentration of cholesterol to form niosomes [11]. Surfactants with an HLB outside of this range do not form niosomes. Drug entrapment efficiency of the niosomes is depends on HLB value of surfactant. The HLB value has a plays an important role in the controlling drug entrapment of niosomes. Entrapment efficiency decreases as the HLB value decreases from 8.6 to 1.7 [12].

2.2.2. Critical Packing Parameter (CPP)

During the preparation of niosomes, the geometry of the vesicle depends upon the critical packing parameter (CPP). The molecular geometry of the amphiphiles affect the self-assembly of them and which leads to different form of structures. The shape of nanostructures formed by self-assembly of amphiphilic molecules and effect of surfactants structure in niosomes formation can be predicted by Critical Packing parameter (CPP), a dimensionless scale. A CPP of less than 0.5 indicate the formation of spherical micelles; while a CPP between 0.5 and 1 indicate the formation of bilayer planner and A CPP of greater than 1 indicate the formation of inverted micelles [12] Critical packing parameter depends on the symmetry of the surfactant and can be defined using following equation [13]

$$CPP = V/lc \times a_0$$

Where V is hydrophobic group volume, lc is the critical hydrophobic group length, and a₀ is the area of hydrophilic head group.

2.3. Cholesterol

The most common additive in niosomes formulation is cholesterol, an amphiphilic compound that can cooperate with surfactant to make hydrogen bonding between hydroxyl groups of cholesterol and hydrophilic head of the surfactant. Cholesterol is a lipid molecule, but it is a comparatively rigid molecule and lacks of the accommodating ability of an acyl-chained lipid. Particularly, cholesterol does not form bilayers and its inverted cone shape [8]. However, cholesterol has been called the “mortar” of bilayers because, by virtue of its molecular shape and solubility properties, it fills in void spaces between the amphiphiles, thus making them more rigid into the bilayer structure [11]. The content of cholesterol in niosomes affects their structure as well as physical possessions like drug entrapment performance, long-term stability, payload release, and biostability [14]. The cholesterol has been reported to increase

membrane stability, decrease the fluidity of the membrane and alter membrane permeability. It increases stabilizes niosomes against destabilizing effects which is caused by plasma and serum materials [15, 16].

2.4. Charged Inducing Molecules

One of the approaches used to stabilize niosomes is based on the addition of a charged molecule to the bilayer. Dicapryl phosphate (DCP) and phosphatidic acid are the negatively charged molecules used. Similarly positive charged molecules like stearyl amine (SA) and cetyl pyridinium chloride are commonly used in niosomal preparations for preventing aggregation and coalescence of niosomes by electrostatics repulsion. Normally, the charged molecule is added in niosomal formulation in an amount of 2.5–5 mol% is acceptable. However a rising the concentration of charged molecules can obstruct niosomal formation. It has been reported that zeta (ζ)-potentials above |30| mV are needed for full electrostatic stabilization, potentials between |5| and |15| mV represent the region of limited flocculation; whereas |5| and |3| mV correspond to the maximum flocculation. Thus, particle aggregation is less likely to occur for charged particles (high ζ -potential) due to their electric repulsion [16, 17].

3. TYPES OF NIOSOMES

Different types of niosomes have been reported in the literature. On the basis of vesicular size or number of lamellar layers niosomes are classified in to three classes.

3.1. Small Unilamellar Vesicles (SUVs)

Small unilamellar vesicles (SUVs) are obtained from multilamellar vesicles by several techniques like sonication, extrusion under high pressure and high shear homogenization. These vesicles have an approximate size of 10 to 100 nm. As compared to other types of niosomes, they are less thermodynamically stable and have poor drug loading capacity for hydrophilic drugs as well as a higher proneness to form aggregates.

3.2. Large Unilamellar Vesicles (LUVs)

In organic solvent lipid can be solubilized and pour into an aqueous buffers. As result spontaneous LUV growth. Large unilamellar vesicles (LUVs) consist of a single bilayer that surrounds the aqueous core. The hydrophilic drug can be encapsulated easily as LUV niosomes have large aqueous compartment. The use of reverse phase evaporation or the detergent solubilisation processes are the best way to prepare LUV. The approximate sizes of these vesicles are 100 to 3000 nm.

3.3. Multilamellar Vesicles (MLVs)

Multilamellar vesicles (MLV) consist of several bilayers that surround the aqueous lipid compartments separately. These vesicles have an approximate diameter of 0.5-10 μm . MLVs are more stable compared to the other two forms of niosomes under normal storage conditions. Due to presence of multiple bilayer membrane, they are favorable for loading of lipophilic drug [18, 19].

4. ADVANTAGES AND DISADVANTAGES OF NIOSOMES

4.1. Advantages of Niosomes

1. Niosomes have better patient compliance and better therapeutic effect than conventional formulations.
2. Niosomes serve as drug depots in the body which release the drug in a controlled manner through its bilayer providing sustained release of the enclosed drug.
3. Niosomes has targeted drug delivery, through niosomes the drug is directly delivered to the target organ or tissues where the therapeutic effect is required. Thereby reducing the dosing frequency of drug.
4. As compared to liposomes, niosomes are osmotically active, chemically stable and have long storage time.

5. Niosomes can be administered via different routes such as oral, parenteral, topical, ocular etc.
6. Niosomes can improve the permeation of drugs through the skin.
7. Niosomes can be used in the delivery of different category of drugs as it has capability to entrap hydrophilic, hydrophobic as well as amphiphilic drugs.
8. They improve the oral bioavailability of poorly soluble drugs.
9. No special precaution and conditions required for the handling of surfactants [20,21].

4.2. Disadvantages of Niosomes

1. Drug entrapment in aqueous suspension of niosomes can result in fusion, aggregation, leaching, or hydrolysis, reducing the shelf life of niosomes dispersion.
2. Method of preparation takes a long time.
3. Drug leakage.
4. Inadequate loading of drug.
5. Special equipment is required formulation of niosomes [22].

5. METHOD OF PREPARATION

In general method preparation of niosomes starts with hydration of nonionic surfactants with hydration medium. However, they are prepared by multiple methods which based on the sizes of the vesicles and their distribution, number of lamellae, entrapment efficiency of the aqueous phase and permeability of vesicle membrane.

5.1. Thin Film Hydration Method

The thin film hydration method is a simple and well known preparation technique. It is also called as hand shaking method. All required vesicle forming components such as surfactant, cholesterol and other additives like charge inducing molecules all are dissolved in organic solvent in a round bottom flask. With the help of rotary evaporator the organic solvent is evaporated at room temperature to obtain a thin film on internal wall of the flask. Drug containing aqueous phase is added to dried thin film with gentle stirring, upon addition thin film get hydrated which leads to formation of niosomes. If drug is hydrophilic, it can be dissolved to the aqueous phase while if drug is hydrophobic, it can be dissolved in organic solvent [23-25].

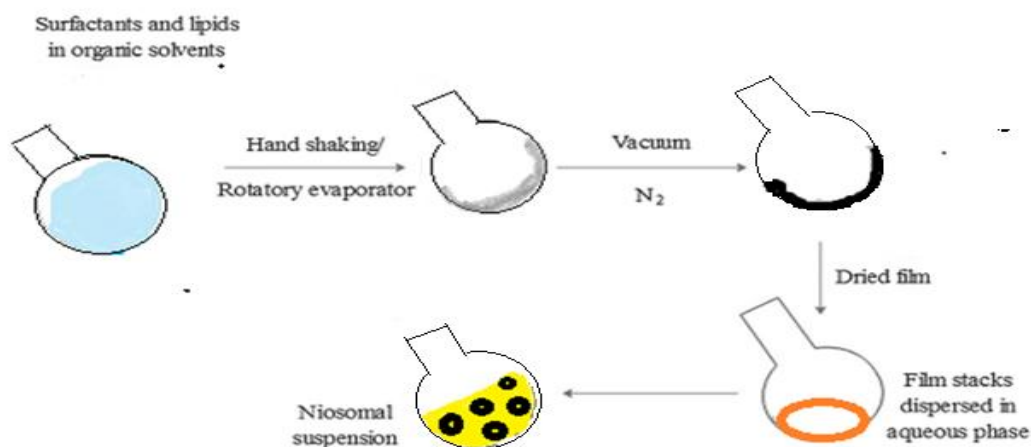


Fig: 02 Schematic diagram of the preparation of niosomes using thin film hydration method [12]

5.2. Ether Ejection Method

In this method surfactant and lipids are dissolved in diethyl ether and then is slowly injected via needle in to a drug aqueous solution which is maintained at constant temperature which is above the boiling point of the organic solvent. Using rotary evaporator organic solvent is removed. During evaporation single layered vesicle is formed [26-28].

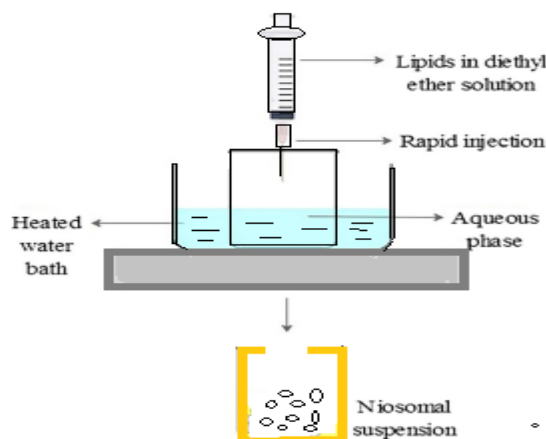


Fig: 03 Schematic diagram of the preparation of niosomes using ether ejection method [28]

5.3. Reverse Phase Evaporation

In this method, surfactant and cholesterol in a 1:1 ratio are mixed in a mixture of ether and chloroform and then add in to an aqueous phase containing drug, as result two immiscible phases are sonicated at 4–5°C. Sonication procedure is continued after the addition of a little quantity of phosphate buffered saline to mixture. The organic solvent is evaporated at 40°C under low pressure. During the evaporation of organic solvents formed niosomes suspension is diluted with phosphate buffered saline and heated in a water bath at 60°C for 10 min to obtain final product of niosomes [29, 30].

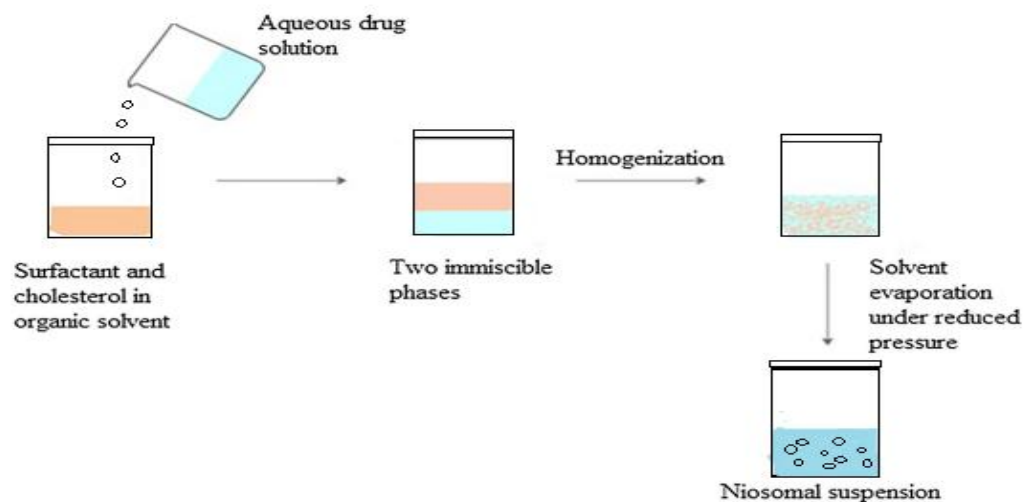


Fig: 04 Schematic diagram of the preparation of niosomes using reverse phase evaporation [19]

5.4. The Bubble Method

The bubble method is single step procedure; without using the organic solvents niosomes can be prepared by sonicating a surfactant, cholesterol and aqueous phase containing drug for 3 min at 70 °C in three necked glass flask, the dispersion is mixed with the help of homogenizer, after that flask is kept in water bath followed by nitrogen gas is passed through dispersion which leads to large unilamellar vesicles [31].

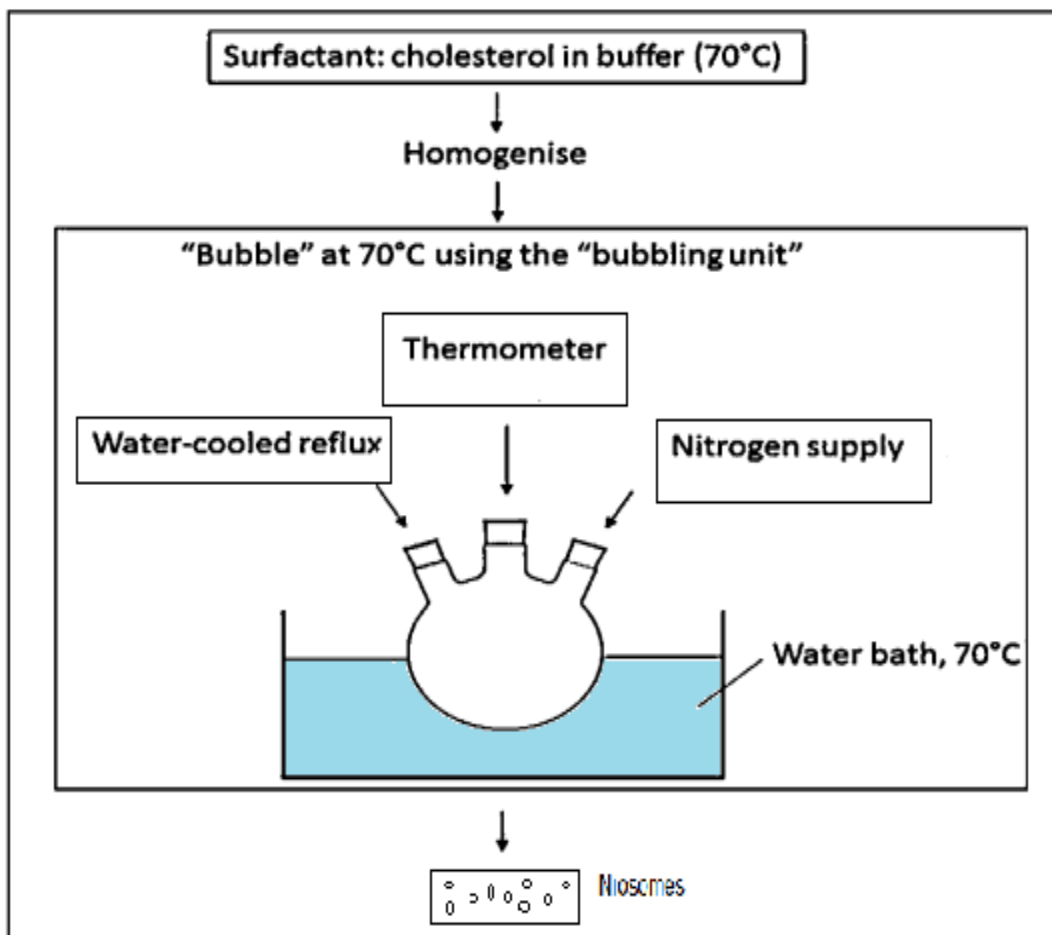


Fig: 05 Schematic diagram of the preparation of niosomes using reverse phase evaporation [30].

5.5. Sonication

In this method drug solution in buffer is mixed with mixture of surfactant and cholesterol, is sonicated with the help of titanium probe sonicator at 60°C for 3 minutes to obtain niosomes. This method is also useful to prepare small unilamellar vesicles from large multilamellar vesicles which are prepared by other methods [32].

6. NIOSOMES AS A TARGETED DRUG CARRIERS

Niosomes are an effective means of targeted delivery of drugs to targeted organ and tissues. Niosomes are very hopeful carriers for the delivery of number pharmacological and diagnostic agents. Many researchers have been reported the method of preparation, characterization, and use of niosomes as drug carriers. Due to presence of nonionic surfactant, they have less toxicity and greater bioavailability. In recent year, targeted drug delivery from niosomes has been studied in various disease models, with existing efforts focusing on protocol optimization, novel compositions, and final formulations [33, 34].

6.1. Anticancer Drug Delivery

The chemotherapy is the current treatment for cancer. The therapeutic effect of many anticancer is decreased due to low penetration of drug in to tumor tissues and due to sever side effect on healthy tissues. These drawbacks can be overcome by including niosomes as a targeted drug delivery.

6.1.1. Breast Cancer

Recently, tamoxifen citrate niosomes were prepared by thin film hydration method for cancer therapy. The optimized niosomal formulation of tamoxifen showed significantly increased cellular uptake (2.8-fold) and showed significantly greater cytotoxic activity on MCF-7 breast cancer cell line [35]. Moreover Cantharidin loaded niosomes were prepared by injection method. The potential antitumor activity of optimized niosomes formulation was evaluated on MCF-7 human breast cancer cell line [36 37].

6.1.2. Ovarian Cancer

Uchegbu et al who formulated the doxorubin loaded niosomes. A human ovarian cancer cell line was used for the activity study of doxorubin loaded niosomes. The result showed that, slight decrease in IC₅₀ against the resistant cell line while the drug was encapsulated in Span 60 niosomes in comparative to the free drug in solution [38].

6.1.3. Melanoma

Artemisone is a 10-amino-artemisinin derivative shows anticancer as well as antimalarial activity. Dwivedi et al. was prepared artemisone loaded niosomes by thin-film hydration method. The optimized formulation showed highly selective cytotoxicity towards the melanoma cells with negligible toxicity towards the normal skin cells [39].

6.2. Targeted Drug Delivery

Niosomes as Nanocarrier targeted drug delivery vesicles which enhance absorption of some drugs via cell membranes and cellular uptake through endocytosis and so localized the drug in tissues and targeted organs and also helps to avoid the reticuloendothelial system, for tumor therapy the efficiency and especially the specificity of cellular targeting of niosomal drug delivery system can be improved by active targeting through use of ligand couple to the surface of niosomes. Niosomes surface can be associate with micromolecules or macromolecular targeting ligands to empower specific cell targeting. Peptide, protein, carbohydrates antibodies and antibodies fragments are commonly molecules that can be bind on targeted cell surface [40].

Tavano et al. was prepared doxorubin loaded Niosomes from a mixture of pluronic L64 as a surfactant by thin film hydration method. During the preparation, transferrin has conjugated to niosomes surface using EDC (N-[3-(dimethylamino) propyl]-Nethylcarbodiimide hydrochloride) chemistry. The anticancer activity of doxorubicin loaded niosomes was evaluated against MCF-7 and MDA-MB-231 tumor cell lines, and result showed a significant decrease in viability in a dose [41].

7. NIOSOMES DRUG DELIVERY STRATEGIES

The Various routes have been reported for the administration of niosomes. Depending on the nature of drugs, surfactants, sickness or locations of disorder, different routes of administration exist for niosomal drugs, including intravenous, intramuscular, dental, ocular, subcutaneous, pulmonary, and transdermal.

7.1. Oral Route Delivery

The oral route is most common preferred route for delivery of therapeutically active substance. Although due to presence of acid and digestive enzyme in stomach, drug can be degrade. Also Environmental factors that affect drug integrity and absorption include segment duration, pH, mucus thickness, residence drug, and bacterial diversity/population in different segments. However, niosomes have been reported as imaginable nonionic vesicles to deliver drug molecules to the desired mucous membrane or skin layers [42].

7.2. Topical Route

7.2.1. Ocular Route Delivery

The physicochemical properties of the drug and vehicle are the crucial factors for the penetration of drug into eyes. However, there are various anatomical and physiological barriers like exclusive tight junctions of corneal epithelium and precorneal tear film that prevent absorption of the administered drug from residing on the eye surface for deeper sites. Therefore, the drugs administrated by ocular route from simple solutions, the bioavailability are less than 5% and often less than 1%. Niosomes can provide prolonged duration of action at the corneal surface by preventing ocular metabolism by enzymes in the lachrymal fluid. Due to this reasons, niosomes have achieved popularity in ocular drug delivery research and are considered as a potential delivery system for the effective treatment of glaucoma and various other diseases [43, 44].

7.2.2. Transdermal Delivery

The stratum corneum barrier is the major obstacles in the topical delivery of drug. Niosomes loaded drug deliver through the skin is beneficial in the drug, which penetrate through the skin and reach in to the systemic circulation. Niosomes are the best nonionic vesicular system for transdermal delivery because they act as a reservoir of drug for a prolonged period of time and enhance skin penetration [46, 47]. Thus estradiol loaded niosomes were prepared with the inclusion of cholesterol facilitated estradiol transdermal penetration [48]. Aceclofenac niosomal gel showed a high cumulative drug penetration and steady state transdermal flux as compared to a plain gel formulation [49].

7.3. Intravenous Route

Niosomes can be delivered by the intravascular route. The benefit of administering the drug through i.v. route is that drug reaches directly into the systemic circulation; apart from this niosomes enhances the stability of drug and prolong its duration in the blood. The intravenous route is used for the delivery of niosomes of numerous drugs. He et al prepared PEGylated niosomes of paeonol to enhance its stability and bioavailability. PEGylated niosomes have the capability of opposing the uptake from mononuclear phagocytic system and thus improves circulation time [50, 51].

7.4. Intramuscular Route

Niosomes can also be administered by using intramuscular route. Jitender Singh Wilkhu was prepared niosomes for the delivery of subunit flu antigen for oral as well as intramuscular delivery [52].

Table No 01: Drugs used in Niosomal Delivery [34]

Sr. No	Route of Administration	Example of Drug
1	Nasal Route	Sumatriptan
2	Transdermal Route	Piroxicam, Nimesulide, Estradiol
3	Intravenous Route	Doxorubicin, Insulin, Rifampicin
4	Ocular Route	Cyclopentol

Table No 02: Niosomes in Targeted Drug Delivery [34]

Sr. No	Targeted Tissue	Loaded Therapeutics Agent	Composition	Preparation Method	Surface Modification	Targeting Molecules
1	Brain	Doxorubicin	Span 60, cholesterol, solulan C24, N- palmitoyl glucosamine	TLE Paddle Method	-	N- Palmitoyl glucosamine
		Dynorphin-B	Span 60, cholesterol, solulan C24, N- Palmitoyl glucosamine	Sonication	-	N- Palmitoyl glucosamine
		Vasoactive Intestinal Peptide	Span 60, cholesterol, solulan C24, N- palmitoyl glucosamine	Sonication	-	N- Palmitoyl glucosamine
2	Breast Cancer	Doxorubicin	Oxidative pluronic L64, cholesterol	Thin film hydration method	EDC Chemistry	Transferrin
3	Chronic Myelogenous	Doxorubicin	Tween 60, pluronic L64	Thin film hydration method	-	Magnetic
4	Melanoma	Doxorubicin	Span 60, cholesterol, Dicetyl phosphate, N-lauryl glucosamine	Ethanol injection method	-	N- Lauryl glucosamine
5	Epidermoid carcinoma	Hydroxycamptothecin	Span 60, cholesterol	Thin film hydration method	Periodate Oxidative	Transferrin
		Doxorubicin	Span 60, cholesterol, solulan C24, N- palmitoyl glucosamine	Sonication	-	N- Lauryl glucosamine

8. CONCLUSION

In the recent years, attentions have been attracted towards vesicular drug delivery systems such as liposomes and niosomes. Niosomes drug delivery system is an effective approach towards novel drug delivery. Niosomes are consisting mainly of non-ionic surfactants and cholesterol. Niosomes may be prepared by various methods. Niosomes offer different advantages over other drug delivery system and have found applicability in pharmaceutical field. Overall, niosomes are a very powerful tool for drug delivery and targeting of many therapeutically active substances. They have the great potential to give better treatment than conventional drug delivery systems. Niosomes have been designed to treat a wide range of chronic diseases with less side effects and improved patient compliance. Niosomes present a convenient, prolonged, targeted and effective drug delivery system with ability of loading both hydrophilic and lipophilic drugs. Thus, these areas need to be further exploration and research so as to prepare out commercially available niosomal formulation.

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