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Theranostic approach of Niosome for management of various diseases: A review

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ABSTRACT

In the past ten years, there has been a significant increase in the publication of review articles and research papers on niosomes, indicating the growing interest of researchers in this field. Niosomes are vesicular carrier systems formed by the self-assembly of non-ionic surfactants. The formation of niosomes is influenced by various factors such as the type of non-ionic surfactant, preparation methods, hydration temperature, and more. In recent times, researchers have found that niosomes hold the potential to enhance the bioavailability of drugs and serve as a novel approach for delivering various therapeutic agents, including chemical drugs, protein drugs, and gene materials. Niosomes are particularly advantageous due to their low toxicity and efficient targeting capabilities. One notable advantage of niosomes over liposomes is their superior stability during the formulation process and storage. This review article aims to provide comprehensive information about niosomes, including different preparation methods, types of niosomes, factors influencing their formation, characterization techniques, applications and recent advancements in niosomal research. The article also includes a literature review of research conducted in the past decade, encompassing the latest developments in the field of niosomes.

KEYWORDS: Niosome, vesicular carrier, non-ionic surfactant, stable.

I. INTRODUCTION

In recent times, there has been a growing focus on developing innovative drug delivery systems that aim to meet two essential criteria: delivering the medication at a rate tailored to the patient throughout the treatment duration and targeting the drug to the specific site of action where it is required. Unfortunately, conventional dosage forms, including prolonged-release formulations, are currently unable to meet these criteria [1]. Novel drug delivery approaches strive to achieve sustained drug effects by either maintaining a predetermined release rate or by ensuring a constant and effective level of the active pharmaceutical ingredient (API) in the body. This approach helps minimize unwanted side effects by avoiding fluctuations in drug concentration. Additionally, NDDS aims to achieve localized drug effects by placing controlled-release systems adjacent to or within the affected tissue or organ. This targeted spatial placement enables precise drug delivery and reduces systemic exposure. Another strategy involves using carriers or chemical modifications to specifically target particular cell types, thereby enhancing the drug's effectiveness [2]. The development of NDDS offers several potential benefits. By providing controlled and sustained drug release, these systems can improve patient adherence by reducing the frequency of administration. This controlled release also allows for better management of chronic conditions and enhances therapeutic outcomes. Various examples of novel drug delivery systems include liposomes, nanoparticles, microparticles, hydrogels, implantable devices, and drug-eluting stents [3]. Each system possesses unique characteristics and mechanisms to achieve controlled release and targeted delivery.

Vesicular systems have emerged as a valuable strategy for targeted drug delivery and have shown promise in improving outcomes. Lipid-based

vesicles in particular have found diverse applications in fields of genetic engineering and immunological research, diagnosis [4]. Vesicles are frequently utilized to imitate biological membranes as well as for attaining targeted delivery of API.
Biological membranes play a fundamental role in cellular organization by surrounding and compartmentalizing cells and organelles. All biological membranes share a defining characteristic i.e the bilayer arrangement of lipids. Studying the motional dynamics and static structures of isolated compartments inside biological membranes and lipid vesicles requires careful attention to experimental design. These experimental models were primarily created for fundamental research, but they have contributed significantly to technological improvement. Lipid carriers have been shown to be successful delivery systems for controlled drugs [1].
Niosomes are vesicular systems made of nonionic surfactants instead of phospholipids that self-assemble in aqueous solutions with the help of physical agitation or high temperatures [5 6]. The surfactants used for fabricating niosomes are tweens, spans, and ethoxylated alcohol that are stabilized by adding cholesterol as well as trace quantities of ionic substances like chitosan or diacetyl phosphate[7]. Liposomes come up with many drawbacks such as insufficient chemical stability, the propensity of phospholipids for oxidation, high production costs, and demand for specialized handling and storage conditions. These limitations can be overcome by the use of nonionic surfactants as membrane-forming constituents instead of phospholipids [8]. Their unique design, which includes an inner aqueous compartment surrounded by a hydrophobic membrane, enables the inclusion (and, correspondingly, codelivery) of hydrophobic and hydrophilic drugs [3 9].

Over the years, nanomaterials have gained attention in tumor treatment due to their active and passive targeting abilities. While there are various drugs used for cancer therapy, their sensitivity often leads to inadequate results and can cause unwanted side effects, including damage to healthy cells. To address these challenges, researchers have explored different forms of nanomaterials such as liposomes, polymers, molecules, and antibodies. The aim is to combine these nanomaterials in cancer drug design to achieve a balance between increasing efficacy and reducing drug toxicity [10].Niosomes, in particular, have been studied as promising carriers for poorly absorbable drugs, including vinpocetine and simvastatin, with the goal of improving their oral bioavailability and gastrointestinal absorption [9 11 12]. However, niosomes do have some drawbacks. These include the potential for aggregation, leakage, and hydrolysis of the drug, as well as fusion of vesicles [13]. Additionally, the aqueous suspension of niosomes can lead to hydrolysis of the drug within the structure.

In summary, nanomaterials, including niosomes, hold promise in cancer drug design by enhancing drug delivery and reducing toxicity. However, challenges such as drug instability and hydrolysis within the niosomes need to be addressed to maximize their effectiveness as drug carriers. The high stability of the niosomes made the formulation processes much simpler. Niosomes are also substantially less expensive than liposomes. Niosomes can also be manufactured for a variety of formulations for usage in various therapeutic applications. For instance, research that examined revolutionary nano-vesicle-based niosomes for the inhalation therapy of pulmonary disorders finished its Phase I trial in 2017. Melatonin niosome oral gel was developed to address the issues of stability and absorption. Clinical research will be used to assess their pharmacokinetic characteristics, sleep-inducing efficacy, and adverse effects[14]. This study introduces the structure, components, and formulation techniques of niosomes and discusses their prospective clinical uses based on these advancements and the benefits of niosomes.

II. STRUCTURE OF NIOSOME

Niosomes are spherical structures consisting of microscopic lamellar formations, which can be unilamellar or multilamellar in nature [14]. The bilayer of niosomes is composed of nonionic surfactants, either with or without the inclusion of cholesterol and a charge inducer. Different combinations and molar ratios of surfactants are used to form niosomes. The presence of proper amount of cholesterol helps maintain the rigidity of the bilayer, resulting in less permeability and efficient interaction with surfactant [15]. Charge inducers play a role in providing charge to the vesicles, leading to an increase in vesicle size and enhancing the entrapment efficiency of drugs. Both negative and positive charge inducers contribute to stabilizing the vehicles. In niosomes, nonionic surfactants tend to arrange themselves with their hydrophilic ends facing outward towards the aqueous phase, while the hydrophobic ends face inward, forming a closed bilayer structure that encapsulates solutes within an aqueous solution [16]. This closed bilayer structure consists of hydrophilic inner and outer surfaces, with a lipophilic core

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sandwiched in between. The formation of this closed bilayer structure requires energy such as heat or physical agitation. Niosomes can be classified into three groups based on their vesicle size: small unilamellar vesicles, multilamellar vesicles, and large unilamellar vesicles [17].

III. COMPONENTS OF NIOSOME

a. Non-ionic surfactant

Nonionic surface-active agents, which consist of a polar head and a nonpolar tail, serve as the fundamental components in the preparation of niosomes. These agents exhibit amphiphilic properties, meaning they have both hydrophilic (polar) and hydrophobic (nonpolar) regions. The polar head of the nonionic surfactant interacts with water or other polar solvents, while the nonpolar tail avoids contact with the aqueous environment. This amphiphilic nature allows nonionic surfactants to form the essential bilayer structure of niosomes by arranging themselves in a way that the polar heads face the aqueous phase while the nonpolar tails remain shielded within the bilayer core [15]. Nonionic surfactants used in niosome preparation offer several advantages over anionic, cationic, and amphoteric surfactants. These nonionic surfactants do not carry an electrical charge, making them more stable, compatible, and less toxic. Compared to other types of surfactants, nonionic surfactants exhibit reduced hemolysis and irritation on cellular surfaces. Nonionic surfactants have various applications, including enhancing permeability, improving solubility, serving as wetting agents, and acting as emulsifiers. Their ability to enhance permeability can be beneficial for drug delivery, as it allows drugs to penetrate biological barriers more efficiently. Moreover, nonionic surfactants possess the property of inhibiting p-glycoprotein, a protein that pumps drugs out of cells, thus potentially increasing the absorption and targeted delivery of anticancer drugs [18 19]. Hydrophilic lipophilic balance and Critical packaging parameters are the important parameters before the selection of surfactants. It plays an important role in obtaining controlled entrapement efficiency. Until date, a variety of non-ionic surfactants with different HLB values have been utilised depending on the delivery of niosomes, including polyglycerol alkylethers, glucosyl dialkyl ethers, crown ethers, polyoxyethylene ethers, and esters like the Brij, Span, and Tween series [20]. Another significant aspect that may have an impact on the entrapment efficiency is the temperature of the phase transition. For instance, the high entrapment efficiency of span 60 may be related to its high transition temperature [16 21]. Iodides, mercury salt, salicylates, sulfonamides, and tannins, phenolic compounds are not utilised with surfactants with gel transition temperatures less than 10 °C because they can induce oxidation [17].

The area of the polar head group, as well as the volume and length of the non-polar group, may be used to determine a surfactant's CPP value. The type of vesicle that will develop may be predicted using CPP values.

b. Cholesterol

Cholesterol plays a crucial role in the creation of niosomes. Although it is not necessary for the development of a niosome but it has a significant impact on many of the niosome's features. It may have an impact on the membrane's permeability and stiffness, entrapment effectiveness, stability, duration spent in storage, and toxicity of freeze-dried niosomes. When cholesterol is combined with low HLB surfactants, the vesicle's stability can be improved, and when the HLB value is more than 6, bilayer vesicles can form. The preparation becomes more stiff as a result of the addition of cholesterol [22]. Shea butter can be substituted for cholesterol but has a lower niosome entrapment effectiveness.

c. Charged Molecule

In order to strengthen the stability of niosomes and inhibit coalescence by electrostatic repulsion, certain charged molecules are added to them. Phosphatidic acid and diacetyl phosphate (DCP) are the chemicals that are employed that are negatively charged. Similar to STR, the well-known positively charged compounds employed in niosomal preparations include stearyl pyridinium chloride and stearyl amine. The fundamental purpose of these electrically charged molecules is to stop niosome aggregation. Charged molecule concentrations are only acceptable in the range of 2.5 to 5 mol% since higher concentrations can prevent the development of niosomes [23 24].

d. Hydration Temperature:

The temperature of hydration has an impact on the niosome's size and form. The ideal hydration temperature is higher than the temperature at which gel transitions to liquid. The assembly of surfactants into vesicles and vesicle shape alteration are both impacted by changes in temperature. The change is also due to hydration duration and hydration medium volume [25].

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IV. PREPARATIONAL METHODS:

a. *Reverse Phase Evaporation Technique*

To prepare niosomes, cholesterol and surfactant are combined in a 1:1 ratio and dissolved in a mixture of organic solvents such as ether and chloroform. The resulting mixture is then combined with an aqueous solution of the desired drug, forming a water-in-oil emulsion. The emulsion is subjected to sonication at a temperature of 4-5ºC. This sonication process helps in the formation of small vesicles within the emulsion. To further refine the niosomal suspension, small amounts of phosphate buffered saline (PBS) are added and the mixture is sonicated again. The organic phase is then removed by subjecting the suspension to a lower pressure at a temperature of 40ºC. To achieve the final formation of niosomes, the diluted suspension is heated on a water bath at a temperature of 60ºC for a duration of 10 minutes. This heating process helps in the formation of well-defined niosomes [24 26 27]

b. *Ether Injection Method*

In this method, a solution consisting of a specific ratio of cholesterol and surfactant dissolved in ether is slowly injected into an aqueous solution containing the desired drugs. The aqueous solution is preheated and maintained at a temperature of 60 °C, and the injection is performed using a designated gauze needle. As the ether vaporizes, unilamellar vesicles composed of the surfactants and drug are formed.

Subsequently, fluorinated hydrocarbons can be used instead of ether, especially for drugs sensitive to high temperatures. Fluorinated hydrocarbons have lower vaporization temperatures, allowing for the formation of vesicles without subjecting the drugs to excessive heat. The size of the resulting niosomes using this method typically ranges between 50 and 1000 nm. The actual size is influenced by various formulation variables and experimental conditions, such as the composition of the cholesterol-surfactant mixture, the rate of injection, and the temperature of the aqueous solution. In summary, this method involves the slow injection of a cholesterol-surfactant-ether solution into a preheated aqueous drug solution, leading to the formation of unilamellar vesicles. The size of the resulting niosomes depends on the specific formulation parameters and experimental setup [28].

c. *Micro fluidization method*

Microfluidization is an advanced technique employed to create unilamellar vesicles with a well-defined size distribution. This method is based on the principle of a submerged jet, where two fluid streams interact at ultra-high velocities within precisely defined microchannels present in the interaction chamber. By arranging the impingement of a thin liquid sheet along a common front, the energy supplied to the system is concentrated within the area where niosomes form. The utilization of microfluidization leads to several advantages in niosome preparation. Firstly, it results in greater uniformity among the vesicles, ensuring a more consistent size distribution. Additionally, the size of the niosomes produced using this technique tends to be smaller, which can be beneficial for certain applications. Lastly, the reproducibility of the niosomes formed through microfluidization is enhanced, allowing for consistent and reliable results. Overall, microfluidization is a recent and efficient method employed to generate unilamellar vesicles with precise size control. By harnessing the submerged jet principle and optimizing the energy distribution, this technique offers improved uniformity, smaller size, and enhanced reproducibility of niosomes [29 30].

d. *Hand shaking method*

To prepare niosomes, the process begins by dissolving cholesterol and surfactant in an organic solvent such as ether, chloroform, or benzene. This mixture is then placed in a round bottom flask and subjected to evaporation under reduced pressure in a vacuum evaporator. The evaporation process removes the solvent, leaving behind a mixture of solid surfactant and cholesterol adhering to the walls of the flask. Next, the solid surfactant and cholesterol layer on the flask walls is rehydrated by adding an aqueous solution containing the desired drug. The mixture is continuously shaken, leading to the swelling of the surfactant layer. As the surfactants swell, they eventually fold and form vesicles, entrapping the drugs within their structures.It is important to note that the amount of liquid volume entrapped within the vesicles is relatively small, typically ranging from 5% to 10% of the total volume. This means that the majority of the vesicle's internal space consists of the bilayer structure formed by the surfactants and cholesterol, with only a small proportion containing the drug solution. In summary, the preparation of niosomes involves dissolving cholesterol and surfactant in an organic solvent, evaporating the solvent, rehydrating the solid surfactant and cholesterol layer with an aqueous drug solution, and ultimately forming vesicles that entrap the drugs. The resulting niosomes have a small internal volume of liquid relative to the vesicle size [31 32].

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e. Sonication Method

To prepare niosomes using this method, a drug solution in buffer is added to a mixture of surfactant and cholesterol in a 10ml glass vial. The vial containing the mixture is then subjected to probe sonication at a temperature of 60°C for a duration of 3 minutes. A sonicator equipped with a titanium probe is used for this process. The probe sonication helps in the formation of niosomes, resulting in the encapsulation of the drug within the vesicles [33]**.** (Sharma , Ali, & Aate, 2018).

f. The Bubble Method

The bubbling unit used in this method consists of a round-bottomed flask with three necks, which is placed in a water bath to regulate the temperature. The first neck is fitted with a water-cooled reflux condenser, while the second neck accommodates a thermometer to monitor the temperature. The third neck is used for the supply of nitrogen gas.To prepare the niosomes, cholesterol and surfactant are combined and dispersed in a buffer solution with a pH of 7.4. The dispersion takes place at a temperature of 70°C. After the surfactant and cholesterol are mixed together for 15 seconds using a high shear homogenizer, the mixture is immediately subjected to a process called "bubbling." During the bubbling process, nitrogen gas is passed through the mixture at a temperature of 70°C. This bubbling action helps in the formation of niosomes, resulting in the encapsulation of the drug within the vesicles.In summary, the preparation of niosomes using this method involves dispersing cholesterol and surfactant in a buffer solution, followed by mixing with a high shear homogenizer. The mixture is then "bubbled" using nitrogen gas at a controlled temperature of 70°C, leading to the formation of niosomes [34].

g. Extrusion Method

To prepare niosomes using this method, a mixture of cholesterol and diacetyl phosphate is first prepared. The mixture is then subjected to solvent evaporation using a rotary vacuum evaporator, resulting in the formation of a thin film. This film consists of the cholesterol and diacetyl phosphate components. Next, the thin film is hydrated by adding an aqueous drug solution to it. The hydration process leads to the formation of a suspension containing the niosomes. To obtain niosomes of uniform size, the suspension is then extruded through a series of polycarbonate membranes. These membranes have a mean pore size of 0.1 mm. The extrusion process involves passing the suspension through the membranes multiple times, typically up to eight passages. This repetitive extrusion helps in achieving a more uniform size distribution of the niosomes. In summary, the method involves preparing a mixture of cholesterol and diacetyl phosphate, evaporating the solvent to form a thin film, hydrating the film with an aqueous drug solution, and then extruding the resulting suspension through polycarbonate membranes to obtain uniform-sized niosomes [35].

V. CHARACTERIZATION OF NIOSOME:

Characterizing niosomes is crucial for understanding their behavior, quality, and potential for future clinical studies. Several characteristics of niosomes, such as size, size distribution, zeta potential, morphology, entrapment efficiency (EE), and in vitro release, significantly impact the vesicle's rigidity and its performance in vivo. Size, EE, and in vitro drug release are among the most important parameters to consider. The size of the niosomes affects their rigidity, and a reasonable vesicle size is desirable for optimal performance. EE refers to the amount of the loaded drug effectively trapped within the niosomes, and it depends on factors such as cholesterol content, properties of the membrane components, and the specific drug being loaded. The method employed to load the drug into the niosome structure also affects the EE rate. Generally, larger vesicles tend to have higher entrapment efficiency as they provide more space to accommodate the active agent. These characterization parameters provide crucial insights into the stability, performance, and efficacy of niosomes. They help determine the suitability of niosomes as drug delivery systems and guide further optimization in their formulation and preparation. By understanding the characteristics of niosomes, researchers can make informed decisions and design niosomal formulations that possess the desired properties for effective drug delivery.

a. Particle size and polydispersive index

Particle size is a crucial component of niosome structure since it provides information on the stability and physical characteristics of the particles. The niosome particle sizes range from around 10 nm to 50 m. There are several ways to measure niosome size, including light scattering methods (DLS) and light microscopy [16]. DLS needs to be transformed into PCS (photon correlation spectroscopy)[36] . Only a little concentration of particle samples are needed for this efficient and non-destructive approach. DLS offers information on particle size dispersion in

addition to cumulative data on average particle size[37] . There are also other methods employed, including freeze-fracture replication-electron microscopy (FF-TEM), TEM, and electron microscopic analysis (SEM). Niosome size and the number of bilayers may both be determined using electron microscopic methods[38]. It should be noted that microscopy methods produce artefacts in general. As a result, it is advised to use a variety of techniques to get accurate findings.

b. Morphological representation

Microscopic techniques are commonly employed to examine the particle shape and structure of niosomes. Liquid samples are typically analyzed using electron microscopy, transmission electron microscopy (TEM), and ice fracture transmission electron microscopy (FF-TEM). On the other hand, solid samples are best studied using scanning electron microscopy (SEM) techniques [37].

c. Zeta potential

One of the key elements in identifying niosome particles is their surface charge, or zeta potential, which offers information on the solidity of the niosome structure. Typically, charged niosome stability compared to those of uncharged niosomes, the resistance to fusion and aggregation is stronger [39]. The zeta potential, which measures the electrostatic interaction between nanoparticles, can be determined using the laser Doppler velocimetry technique. Research indicates that a zeta potential above 30 mV or below 30 mV signifies satisfactory stability. This technique allows for assessing the electrostatic properties of nanoparticles and their potential for maintaining stable colloidal suspensions [40].

d. Formation of bilayer

Niosomes exhibit two types of structures: unilamellar and multilamellar. The arrangement of surfactants into bilayers can be studied by observing X-cross formation under light polarization microscopy. This technique helps in characterizing the formation and organization of the lipid bilayers within niosomes, providing valuable insights into their structural properties [41].

e. Hydration temperature

The size and shape of niosome vesicles are influenced by the temperature of hydration. Optimal conditions occur when the hydration temperature is above the gel to liquid-phase transition of the system. Lowering or raising the temperature has an impact on the organization of surfactants and the overall morphology of the niosomes. Therefore, careful control of hydration temperature is essential to achieve desired niosome characteristics [42].

f. Stability

The stability of vesicular niosomal bilayer systems is influenced by various factors including physical, biological, and chemical aspects. The stability of niosomes plays a crucial role in determining their functionality both in vitro and in vivo. Physical stability refers to the ability of niosomes to maintain their structural integrity over time, while biological stability refers to their ability to withstand biological environments and interactions. Chemical stability, on the other hand, relates to the resistance of niosomes against degradation or chemical reactions. Overall, the stability of niosomes directly impacts their performance and effectiveness in different applications, highlighting the importance of maintaining their stability for desired outcomes [43]. We can demonstrate potential instability by examining the size and zeta potential and altering these two variables. The stability of niosomes is frequently assessed over a period of 90 days at various temperatures (4 °C, 25 °C, and 40 °C) and in a moderately humid environment [44 45].

g. Entrapement efficiency

Entrapment effectiveness is the most important aspect for the therapeutic usage of niosomes[31] . Centrifugation, gel chromatography, dialysis, or filtering should be used to remove unloaded pharmaceuticals (free drug) from the whole process before to EE measurement. Using 50% n-propanol or 0.1% Triton X-100 at around 1 hour of incubation, the drug trapped in the niosomes is assessed with full removal of the free drug [46] . The concentration of loaded medication in the vesicular structure, also known as entrapment efficiency, may be calculated using the following equation.

$$EE\% = \frac{Total\ entrapped\ drug}{Total\ amount\ of\ drug\ added} \times 100$$

The amount of drug that is trapped in the vesicles makes up the concentration of entrapped drug. The entire dose is equal to the total ratio of the main drug [47].

h. In-vitro **drug release**

One of the key aspects of niosome characterization is the evaluation of in vitro drug release, which is influenced by several factors such as the hydration temperature, drug concentration, and membrane properties. Dialysis membrane is commonly used to study the release rate of active agents (drug molecules). The process involves washing and

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soaking a clean dialysis bag in distilled water, followed by filling it with the niosome-drug mixture and sealing it. The sealed vesicle bag is then placed in a 200-ml glass of phosphate-buffered saline (PBS) at a constant temperature (usually 37 °C) and stirred using a magnetic stirrer. At predetermined time intervals, samples are collected and replaced with an equal volume of freshly prepared medium. These samples are analyzed using suitable methods to determine the amount of drug released over time, such as UV spectroscopy or high-performance liquid chromatography (HPLC) [40 48]. Another method used for in vitro drug release studies is the Franz diffusion cell. In this method, proniosomes are placed in a Franz diffusion cell equipped with a cellophane membrane. A suitable release buffer is selected, and the proniosomes are then subjected to dialysis at room temperature. At specific time points, the samples are withdrawn from the solution, and effective analysis is performed to measure the drug content. Common analytical methods include UV spectroscopy and HPLC. These techniques allow for the assessment of drug release kinetics and the determination of drug release profiles from niosomal formulations [49].

VI. APPLICATION OF NIOSOME IN DIFFERENT FIELDS

a. Protein/peptide delivery

Delivery of protein and peptide drugs through the oral route has always been challenging due to their vulnerability to degradation by the acidic environment and enzymes in the gastrointestinal tract (GIT). However, niosomes offer a protective mechanism for these drugs against proteolytic enzymes [50 33]. In a study by Moghassemi et al.[51] , niosomes of Bovine serum albumin (BSA) were prepared. The formulation was optimized by varying the cholesterol to span 60 M ratios, and the position of the protein in the vesicle was detected using methyl orange and an inverted light microscope. Niosomes coated with trimethyl chitosan were also prepared to enhance the permeation of insulin for oral delivery.

The use of niosomes provides a promising approach to overcome the challenges associated with oral delivery of protein and peptide drugs. By encapsulating these drugs within niosomes, their stability and protection from enzymatic degradation in the GIT can be significantly improved. This opens up new possibilities for effective oral delivery of protein and peptide drugs, including insulin, which traditionally faced obstacles in reaching their target sites intact [52].

b. Drug delivery to Cancer cells

Niosomes can be used to deliver anticancer drugs directly to target sites. This targeting can be achieved through passive mechanisms [53], where the unique properties of tumor cells allow the deposition of niosomes within the tumor but not in normal cells. It can also be achieved through physical methods [54], such as delivering drugs based on specific environmental conditions like pH or magnetic fields. Additionally, active targeting is possible through the active uptake of niosomes by tumor cells [53]. Active targeting can be achieved by modifying the surface structure of the niosomes or attaching ligands to them. The attachment of ligands can be done by incorporating cholesterol-PEG-ligand conjugates into the niosomes or attaching them to cholesterol or the end of the polyethylene glycol chain [55,56].

Researchers have successfully prepared niosomes of paclitaxel for oral delivery, enhancing its bioavailability and stability [31]. PEGylated niosomes of gambogenic acid have been developed as carriers for anticancer therapy, improving the stability of gambogenic acid [57]. Self-degrading niosomes have been prepared for multi-drug delivery [58], encapsulating hydrophobic curcumin and hydrophilic doxorubicin hydrochloride for anticancer treatment. These niosomes exhibited a two-phase release, with doxorubicin released in the initial phase for two days followed by curcumin release for seven days. These niosomes showed enhanced cytotoxic effects against HeLa cell lines. Cationic PEGylated niosomes have been developed for the co-administration of curcumin and paclitaxel, resulting in enhanced synergistic antitumor efficacy[59]. Niosomes of morusin have been prepared to potentiate anticancer therapy, and the release of the drug from these niosomes was found to be pH-dependent. Higher drug release was observed in acidic conditions (pH 4.5) compared to physiological pH (7.4), indicating that niosomes can achieve higher drug release in the acidic environment of cancer cells [60].

c. Antigen /Vaccine delivery

For the oral administration of vaccinations, bilosomes were developed by incorporating bile salt into the bilayer of vesicles. The antigens are shielded by these bilosomes from being broken down by GIT enzymes [61].

d. Haemoglobin delivery

Niosomes possess favorable oxygen-absorbing properties, making them suitable carriers for hemoglobin in the bloodstream [53].

e. Management of HIV-AIDS

Niosomes can be used for the prolonged administration of medications for the treatment of AIDS. Low potency and toxicity are issues with these medications' delivery that might be solved by using a niosomal system. Because of its substantial firstpass metabolism, short biological half-life, dose-dependent haematological toxicity, and low bioavailability, zidovudine, an anti-HIV medication, has limits in its therapeutic effectiveness [62]. According to reports, niosomes can solve zidovudine's drawbacks [25]. A particular reversible HIV protease inhibitor is lopinavir. Its very poor water solubility, extremely high log P value, sensitivity to cytochrome P450 3A4 and vulnerability to P-glycoprotein efflux transporters all restrict its systemic bioavailability when taken orally. Transdermal niosomes were made and compared with the ethosomal gel to address these problems. The findings of ex-vivo skin permeation investigations showed that ethosomal gel deposited drugs into the skin more than niosomal gel did, but that niosomes permeated the skin more deeply and had a superior drug release profile[63] . Niosomes were created to improve the oral bioavailability of tenofovir disoproxil fumarate[64]. They observed a considerable improvement in the medication's mean residence time and a two-fold increase in bioavailability, both of which point to a prolonged release of the drug. Stavudine niosomes were developed for targeted and controlled release.

f. In Leishmaniasis

Research has demonstrated that the utilization of niosomes in the treatment of Leishmaniasis, a disease caused by the invasion of Leishmania parasites into liver and spleen cells, offers several advantages. In tests conducted, it was found that niosomes enabled the administration of higher drug levels without inducing adverse side effects, leading to improved treatment efficacy for Leishmaniasis. [65 66]

g. For imaging

Niosomes may be beneficial for diagnostic imaging of organs like the liver and spleen because they can transport radiopharmaceuticals. Imaging uses DTPA that has been 99mTc labelled [63]. Lobitridol (a diagnostic drug) is employed with niosomes for x-ray imaging [49] . An encapsulated paramagnetic drug has been demonstrated to more effectively target tumours when administered as a conjugated niosomal formulation of gadobenate dimeglumine with [N-palmitoylglucosamine (NPG)], PEG 4400, and both PEG and NPG [67] . By including contrast agents or dyes (near-infrared) in the inner aqueous or non-aqueous compartment or by conjugating onto the surface of niosomes, A.Massotti developed unique biconjugate niosomes for imaging. Gd (EDTA) 2 can be utilised as a contrast agent during integration[68] . Optical imaging combined with magnetic resonance imaging is a crucial technique for the diagnosis of tumours [69] [70,71]. For in-vivo imaging, polyethylene amino groups and near-infrared probes can be combined to get more efficient result.

VII. Conclusion

Niosomes represent an innovative approach to designing effective drug delivery systems at the nano level. They provide a valuable opportunity for encapsulating hydrophilic, lipophilic, or both types of drugs within their structures. Numerous studies have explored the use of different types of niosomes for delivering a variety of drugs, including anticancer agents, anti-inflammatory agents, anti-infective agents, and more. These studies have shown that niosomes can enhance drug stability, reduce required dosage, and enable targeted delivery to specific tissues. Furthermore, the properties and characteristics of niosomes can be further improved through novel preparation, loading, and modification methods tailored for specific administration routes. As a result, niosomes hold great promise as valuable tools in the development of commercially available therapeutics.

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