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A Review on Niosomes Novel Drug Delivery System

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Abstract
The management of infectious illnesses and vaccination practises has experienced a revolutionary change in recent years. With the development of biotechnology and genetic engineering, not only have numerous biologicals targeted at certain diseases been created, but focus has also been placed on the efficient delivery of these biologicals. As an alternative to liposomes, niosomes are vesicles made of non-ionic surfactants that are biodegradable, more harmless, more stable, and less costly. This article examines the present growth and enlargement of interest in niosomes throughout a variety of scientific fields, with a focus on their use in medicine. Additionally, this article gives a general review of niosome preparation methods, niosome kinds, niosome characterization, and niosome applications.

Keywords: Bilayer, drug entrapment, lamellar, niosomes, surfactants

Introduction:
The idea of targeted drug delivery is to concentrate the treatment in the target tissues while lowering the relative concentration of the drug in the non-target tissues. As a result, the medication is concentrated at the desired location. As a result, the medication has no effect on the tissues nearby. Additionally, the localization of the medicine prevents drug loss, resulting in optimum treatment efficacy. Numerous carriers, including immunoglobulin, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, and niosomes, have been utilised to target drugs. (Karim et al., 2010). Among these carriers, niosomes are among the best. Researchers in the cosmetic business were the first to demonstrate in the 1970s that non-ionic surfactants could self-assemble into vesicles. Microscopic lamellar structures known as niosomes (non-ionic surfactant vesicles) are created when non-ionic surfactants of the alkyl or dialkyl polyglycerol ether family are combined with cholesterol (Malhotra & Jain, 1994). Based on their amphiphilic nature, non-ionic surfactants produce a closed bilayer vesicle in aqueous fluids by utilising some energy, such as heat or physical agitation. While the hydrophilic heads of the bilayer stay in contact with the aqueous solvent, the hydrophobic portions are orientated away from it. By adjusting the vesicle's composition, size, lamellarity, tapped volume, surface charge, and concentration, one may alter the vesicle's characteristics. The vesicle is subject to a variety of forces, including van der Waals forces between surfactant molecules, electrostatic interactions between charged groups of surfactant molecules, entropic forces between surfactant head groups, short-acting forces, etc. The vesicular structure of niosomes is kept in place by these pressures. However, the kind of surfactant, the makeup of the medication that is encapsulated, the storage temperature, detergents, the usage of membrane-spanning

lipids, the in-situ interfacial polymerization of surfactant monomers, and the presence of charged molecules all impact the stability of niosomes. Drug molecules having a wide variety of solubilities can be accommodated by the structure's hydrophilic, amphiphilic, and lipophilic moieties. (Karim et al., 2010). These could serve as a depot, gradually releasing the medication. Delaying the clearance of drugs from the bloodstream, shielding them from the biological environment, and limiting their effects to target cells can all enhance their therapeutic efficacy. (BAILLIE et al., 1985).

Bola-surfactant containing noisome is formed of alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (Bola-surfactant)-Span 80-cholesterol (2:3:1 molar ratio) (Kaur et al., 2004). Niosome preparation surfactants should be biodegradable, biocompatible, and non-immunogenic. Proniosomes, a dry substance, may be hydrated right before use to produce aqueous niosome dispersions. the aggregation, fusion, and leakage issues associated with niosomes and contribute to the simplicity of delivery, storage, and dosing (Hu & Rhodes, 2000). In order to fight a variety of illnesses, several pharmacological substances may be able to use niosomal drug delivery. It may also be utilised to build a unique medication delivery system for pharmaceuticals that are not easily absorbed. By overcoming the anatomical barrier of the digestive system through the transcytosis of M cells from Peyer's patches in the intestinal lymphatic tissues, it increases bioavailability. (Jadon et al., 2009). The reticulo-endothelial system absorbs the niosomal vesicles. This type of targeted drug accumulation is used to treat disorders like leishmaniasis, in which parasites infiltrate the liver and spleen cells. (Sheena et al., 1998). Some non-reticulo-endothelial systems like immunoglobulins also recognise lipid surface of this delivery system (Karim et al., 2010). To explore the nature of the immune response sparked by antigens, TNiosomes have been employed. (Brewer & Alexander, 1992). Niosomes can be used as a carrier for haemoglobin(Moser et al., 1989). Oxygen may pass through vesicles, and the haemoglobin dissociation curve can be changed to resemble that of non-encapsulated haemoglobin. The main disadvantage of transdermal administration is the slow absorption of drugs via the skin..(Jayaraman et al., 1996)

Niosome Type:

Niosomes can be categorised into three kinds based on the size of the vesicle. Large unilamellar vesicles (LUV, size=0.10 m), multilamellar vesicles (MLV, size=0.05 m), and tiny unilamellar vesicles (SUV, size=0.025-0.05 m) are the three types.

Methods of Prepration:

Various techniques are used to create niosomes depending on the sizes and distribution of the vesicles, the quantity of double layers, the effectiveness of the aqueous phase's entrapment, and the permeability of the vesicle membrane.

Preparation of small unilamellar vesicles

In a scintillation vial, the drug-containing aqueous phase is mixed with the surfactant and cholesterol combination. (Ge et al., 2019) A sonic probe is used to homogenise the mixture for 3 minutes at 60°C. The vesicles are uniformly tiny and modest in size. Small-scale fluidization Within the interaction chamber, two fluidized streams travel ahead through a properly planned micro channel and interact quickly. (Karim et al., 2010) Here, a common gateway is set up so that energy provided to the system stays inside the region where niosomes are formed. Greater consistency, lower size, and higher repeatability are the outcomes.

Preparation of multilamellar vesicles

In the hand shaking technique, a thin coating of the solid mixture is left on the flask wall after the surfactant and cholesterol have been dissolved in a volatile organic solvent such diethyl ether, chloroform, or methanol in a rotary evaporator. (Baillie et al., 1986). The dried layer is hydrated with aqueous phase containing drug at normal temperature with gentle agitation.

Reverse phase evaporation technique (REV)

In this procedure, a solution of ether and chloroform is used to dissolve the cholesterol and surfactant. (Naresh et al., 1994) This is combined with an aqueous phase that contains a medication, and the combined two phases are then sonicated at 4-5°C. A tiny amount of phosphate buffered saline is added, and then the transparent gel that has formed is further sonicated. Low pressure is used to remove the organic phase at 40 °C. Niosomes are produced by heating the resultant viscous niosome suspension in a water bath at 60°C for 10 minutes before diluting it with phosphate-buffered saline.

AThe ether injection technique is mainly based on slowly injecting niosomal components in ether into a warmed aqueous phase maintained at 60°C using a 14-gauge needle at a rate of around 0.25 ml/min.(Baillie et al., 1986) The delayed vaporisation of the solvent causes an ether gradient to stretch towards the aqueous-nonaqueous boundary, which is most likely what causes the development of bigger unilamellar vesicles. The creation of the bilayer structure may be due to the former. The method's drawback is that it's challenging to get rid of the trace amounts of ether that are usually found in the vesicles suspension.

Miscellaneous

Evaporation creates a thin layer from a surfactant, cholesterol, and diacetyl phosphate combination in chloroform. (Jayaraman et al., 1996)] Aqueous drug solution is used to hydrate the film, and the resulting suspension is extruded through a series of up to eight passes of polycarbonate membranes. Niosome size may be managed well using this technique.

- ***Emulsion method***

TAn organic surfactant, cholesterol, and aqueous medication solution are combined to create the oil in water (o/w) emulsion. (Hao et al., 2002), Niosomes are then disseminated in the aqueous phase when the organic solvent evaporates.

- ***Lipid injection method***

With this technique, a costly organic phase is not necessary. Here, the lipid and surfactant combination is first melted before being injected into a hot, highly agitated aqueous phase that contains dissolved medication. Here, the medicine can be dissolved in molten lipid and the mixture injected into an agitated, heated, and surfactant-containing aqueous phase.

Niosome preparation using Micelle

Enzymes can also be used to create niosomes from a mixed micellar solution. When treated with esterases, a micellar mixture of C16 G2, dicalcium hydrogen phosphate, and polyoxyethylene cholesteryl sebacetate diester (PCSD) transforms into a niosome dispersion. The esterases break down PCSD to produce polyoxyethylene, sebacic acid, and cholesterol. The result is C16 G2 niosomes when cholesterol is combined with C16 G2 and DCP.

Characterisation of niosomes

Niosomal vesicles are thought to be spherical, and the laser light scattering technique may be used to measure their mean diameter.(Blazek-Welsh & Rhodes, 2001) Additionally, the diameter of these vesicles may be measured by optical microscopy, ultracentrifugation, photon correlation microscopy, molecular sieve chromatography, and electron microscopy. (Biswal et al., 2008) and freeze fracture electron microscopy. Niosome freeze-thawing causes an increase in vesicle diameter, which may be due to vesicle fusion throughout the cycle.

Bilayer formation

Under light polarisation microscopy, an X-cross formation identifies the assembly of non-ionic surfactants into a bilayer vesicle.(Manosroi et al., 2003)

Number of lamellae

Small angle X-ray scattering, electron microscopy, and nuclear magnetic resonance (NMR) spectroscopy are used to ascertain this.(Biswal et al., 2008)

Membrane rigidity

The mobility of a fluorescence probe as a function of temperature can be used to evaluate the stiffness of a membrane..(Manosroi et al., 2003)

Entrapment efficiency

Unentrapped drug is isolated after niosomal dispersion is prepared, and the amount of drug still present in niosomes is assessed after full vesicle breakdown using 50% n-propanol or 0.1% Triton X-100 and analysis of the resulting solution using the correct test technique for the drug. (Balasubramaniam et al., 2002) It can be represented as:

Entrapment efficiency (EF) = (Amount entrapped / total amount) × 100

In vitro Release Study

A method of *in vitro* release rate study was reported with the help of dialysis tubing.(Yoshioka et al., 1994). A dialysis bag has been cleaned and put in distilled water to soak. The tubing-based bag was sealed after the vesicle suspension was pipetted inside of it. The vesicle-containing bag was next placed in a 250 ml beaker containing 200 ml of buffer solution, which was constantly shaken at either 25°C or 37°C. The buffer was subjected to many assays, each measuring the drug level at different time periods. Another technique included gel filtration on Sephadex G-50 powder stored in double-distilled water for 48 hours to allow the isoniazid-encapsulated niosomes to expand..(Karki et al., 2008). First, 1 ml of the ready-to-use niosome solution was added to the column's top, and regular saline was used for elution. Isoniazid that is contained within niosomes elutes out first as a somewhat thick, white opalescent solution, then as free medication. A dialysis tube with a sigma dialysis sac connected to one end was filled with separated noisome. A magnetic stirrer was used to agitate the dialysis tube while it was suspended in a phosphate buffer solution with a pH of 7.4. Samples were taken out at predetermined intervals and examined using the high-performance liquid chromatography (HPLC) technique.

- ***In vivo* Release Study**

This study made use of albino rats. Groups were used to split up these rats. Niosomal suspension was administered intravenously (via the tail vein) using the proper disposal syringe for the in vivo investigation.

Choice of surfactants and main additives

A surfactant must have a hydrophilic head and a hydrophobic tail in order to prepare niosomes. One or two alkyl, perfluoroalkyl, or, in certain situations, a single steroidal group may make up the hydrophobic tail..(Uchegbu & Vyas, 1998). The single-chain alkyl tail of ether-type surfactants makes them more hazardous than their dialkyl counterparts. Since ester-linked surfactants are in vivo degraded by esterases to triglycerides and fatty acids, the ester-type surfactants are chemically less stable than ether-type surfactants and the former is less hazardous than the latter..(Uchegbu & Vyas, 1998). For the creation of noisome, surfactants with alkyl chains ranging from C12 to C18 are appropriate. Surfactants from the Span series with an HLB number of 4 to 8 can generate vesicles.

Temperature of hydration

The size and form of the niosome are influenced by hydration temperature. It should be above the system's gel to liquid phase transition temperature for optimal conditions. The assembly of surfactants into vesicles is impacted by temperature changes in the niosomal system, which also cause changes in vesicle shape.(Uchegbu & Vyas, 1998)(Arunothayanun et al., 2000). When heated, a polyhedral vesicle made of C16G2:solulan C24 (91:9) turns into a spherical vesicle at 48 degrees Celsius. However, when cooled from 55 degrees Celsius, the vesicle first creates a cluster of smaller spherical niosomes at 49 degrees Celsius before transforming into polyhedral structures at 35 degrees Celsius. The vesicle created by C16G2:cholesterol:solulan C24 (49:49:2), in contrast, does not change shape when heated or cooled..(Uchegbu & Vyas, 1998). The amount of the hydration medium and the duration of the niosomes' hydration are additional crucial criteria in addition to those already discussed. The construction of weak niosomes or the development of issues with drug leakage may come from the improper selection of these components.

Nature of encapsulated drug

Charge and stiffness of the niosome bilayer are influenced by the physico-chemical characteristics of the medication that is encapsulated. The medication interacts with the head groups of the surfactants and builds the charge that causes mutual repulsion between the surfactant bilayers, increasing vesicle size.(Biswal et al., 2008). The aggregation of vesicles is prevented due to the charge development on bilayer.

Methods of Preparation

In comparison to the ether injection approach (vesicles with a diameter of 50–1,000 nm), the hand shaking method produces vesicles with a diameter of 0.35–13 nm. The Reverse Phase Evaporation (REV) technique can be used to create small niosomes. The microfluidization process produces smaller, more homogenous vesicles.

Resistance to osmotic stress

Niosomes are reduced in diameter when a hypertonic salt solution is added to a suspension of niosomes. In hypotonic salt solution, there is first a delayed release with small vesicle swelling that is likely caused by the inhibition of fluid eluting from vesicles, and then there is a quicker release that may be caused by mechanical loosening of vesicles structure under osmotic stress.(ROGERSON et al., 1988).

Conclusion:

Small molecules including proteins and vaccines have been endorsed as a prominent class of medicinal agents as a consequence of recent advances in scientific study. However, they present a number of drug-related difficulties, including low bioavailability, adequate drug administration methods, chemical and physical instability, and possibly dangerous side effects. Niosomes have been criticised for being ineffective in delivering proteins and biologicals, however they are capable of encapsulating deadly medications like those for AIDS, cancer, and viruses. In contrast to ionic drug carriers, which are generally harmful and inappropriate, it offers a viable carrier system. The niosome technology, however, is still in its infancy. As a result, research is being done to create a technology that is appropriate for mass manufacturing since it is a promising approach for delivering tailored medications.

References:

1. Arunothayanun, P., Bernard, M. S., Craig, D. Q. M., Uchegbu, I. F., & Florence, A. T. (2000). The effect of processing variables on the physical characteristics of non-ionic surfactant vesicles (niosomes) formed from a hexadecyl diglycerol ether. *International Journal of Pharmaceutics*. https://doi.org/10.1016/S0378-5173(00)00362-8
2. Baillie, A. J., Coombs, G. H., Dolan, T. F., & Laurie, J. (1986). Non-ionic surfactant vesicles, niosomes, as a delivery system for the anti-leishmanial drug, sodium stibogluconate. *Journal of Pharmacy and Pharmacology*. https://doi.org/10.1111/j.2042-7158.1986.tb04623.x
3. BAILLIE, A. J., FLORENCE, A. T., HUME, L. R., MUIRHEAD, G. T., & ROGERSON, A. (1985). The preparation and properties of niosomes—non-ionic surfactant vesicles. *Journal of Pharmacy and Pharmacology*. https://doi.org/10.1111/j.2042-7158.1985.tb04990.x
4. Balasubramaniam, A., Kumar, V. A., & Pillai, K. S. (2002). Formulation and in vivo evaluation of niosome-encapsulated daunorubicin hydrochloride. *Drug Development and Industrial Pharmacy*. https://doi.org/10.1081/DDC-120015351
5. Biswal, S., Murthy, P. N., Sahu, J., Sahoo, P., & F, A. (2008). Vesicles of Non-ionic Surfactants (Niosomes) and Drug Delivery Potential. *International Journal of Pharmaceutical Sciences and Nanotechnology*. https://doi.org/10.37285/ijpsn.2008.1.1.1
6. Blazek-Welsh, A. I., & Rhodes, D. G. (2001). Maltodextrin-based proniosomes. *AAPS PharmSci*. https://doi.org/10.1208/ps030101
7. Brewer, J. M., & Alexander, J. (1992). The adjuvant activity of non-ionic surfactant vesicles (niosomes) on the BALB/c humoral response to bovine serum albumin. *Immunology*.
8. Ge, X., Wei, M., He, S., & Yuan, W. E. (2019). Advances of non-ionic surfactant vesicles (niosomes) and their application in drug delivery. In *Pharmaceutics*. https://doi.org/10.3390/pharmaceutics11020055
9. Hao, Y., Zhao, F., Li, N., Yang, Y., & Li, K. (2002). Studies on a high encapsulation of colchicine by a niosome system. *International Journal of Pharmaceutics*. https://doi.org/10.1016/S0378-

5173(02)00301-0
10. Hu, C., & Rhodes, D. G. (2000). Proniosomes: a novel drug carrier preparation. *International Journal of Pharmaceutics*.
11. Jadon, P. S., Gajbhiye, V., Jadon, R. S., Gajbhiye, K. R., & Ganesh, N. (2009). Enhanced oral bioavailability of griseofulvin via niosomes. *AAPS PharmSciTech*. https://doi.org/10.1208/s12249-009-9325-z
12. Jayaraman, S. C., Ramachandran, C., & Weiner, N. (1996). Topical delivery of erythromycin from various formulations: An in vivo hairless mouse study. *Journal of Pharmaceutical Sciences*. https://doi.org/10.1021/js960040u
13. Karim, K., Mandal, A., Biswas, N., Guha, A., Chatterjee, S., Behera, M., & Kuotsu, K. (2010). Niosome: A future of targeted drug delivery systems. In *Journal of Advanced Pharmaceutical Technology and Research*. https://doi.org/10.4103/0110-5558.76435
14. Karki, R., Mamatha, G. C., Subramanya, G., & Udupa, N. (2008). Preparation, characterization and tissue disposition of niosomes containing isoniazid. *Rasayan Journal of Chemistry*.
15. Kaur, I. P., Garg, A., Singla, A. K., & Aggarwal, D. (2004). Vesicular systems in ocular drug delivery: An overview. In *International Journal of Pharmaceutics*. https://doi.org/10.1016/j.ijpharm.2003.09.016
16. Malhotra, M., & Jain, N. K. (1994). Niosomes as drug carriers. In *Indian Drugs*. https://doi.org/10.1201/9781003277361-3
17. Manosroi, A., Wongtrakul, P., Manosroi, J., Sakai, H., Sugawara, F., Yuasa, M., & Abe, M. (2003). Characterization of vesicles prepared with various non-ionic surfactants mixed with cholesterol. *Colloids and Surfaces B: Biointerfaces*. https://doi.org/10.1016/S0927-7765(03)00080-8
18. Moser, P., Marchand-Arvier, M., Labrude, P., Handjani-Vila, R. M., & Vigneron, C. (1989). [Hemoglobin niosomes. I. Preparation, functional and physico-chemical properties, and stability]. *Pharmaceutica Acta Helvetiae*.
19. Naresh, R. A. R., Pillai, G. K., Udupa, N., & Chandrashekar, G. (1994). Anti-inflammatory activity of niosome encapsulated diclofenac sodium in arthritic rats. *Indian Journal of Pharmacology*.
20. ROGERSON, A., CUMMINGS, J., WILLMOTT, N., & FLORENCE, A. T. (1988). The Distribution of Doxorubicin in Mice Following Administration in Niosomes. *Journal of Pharmacy and Pharmacology*. https://doi.org/10.1111/j.2042-7158.1988.tb05263.x
21. Sheena, I. P., Singh, U. V., Kamath, R., Uma Devi, P., & Udupa, N. (1998). Niosomal withaferin A with better antitumor efficacy. *Indian Journal of Pharmaceutical Sciences*.
22. Uchegbu, I. F., & Vyas, S. P. (1998). Non-ionic surfactant based vesicles (niosomes) in drug delivery. *International Journal of Pharmaceutics*. https://doi.org/10.1016/S0378-5173(98)00169-0
23. Yoshioka, T., Sternberg, B., & Florence, A. T. (1994). Preparation and properties of vesicles (niosomes) of sorbitan monoesters (Span 20, 40, 60 and 80) and a sorbitan triester (Span 85). *International Journal of Pharmaceutics*. https://doi.org/10.1016/0378-5173(94)90228-3