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Review article

Non- ionic surfactant vesicles and their therapeutics potentials

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Abstract

Niosomes are a novel drug delivery system in which drug is encapsulated in vesicles. Niosomes are non-ionic surfactant vesicles that have potential applications in the delivery of hydrophilic and hydrophobic drugs. Niosomes proved to be a promising drug carrier and has potential to reduce the side effects of drugs and increased therapeutic effectiveness in various diseases. The success of Niosomes as drug carriers has been reflected in a number of surfactant -based formulations, which are commercially available or are currently undergoing clinical trials. This review is mainly focused on the diseases that have attracted most attention with respect to niosome drug delivery. This vesicular drug delivery system having lots of advantage over other type of drug delivery system. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug Efficacy as compared with that of free drug.

Key words: Niosomes, Drug carrier, cancer therapy, Therapeutic application.

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1. Introduction

Non-ionic surfactant vesicles (or niosomes) are now widely studied as alternates to liposomes[1]. They are prepared with various ionic amphiphiles such as dicetylphosphate, stearylamine, etc [2,3,4].

Niosomes are non-ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solution of solute(s) in entirely enclosed by membrane resulted from the organization of surfactant macro-molecules as bilayers. Similar to liposomes, niosomes are formed on hydration of non ionic surfactant film[5]. Colloidal particulate carriers such as liposomes[6] or niosomes[7] as drug delivery systems have distinct advantages over conventional dosage forms. These carriers can act as drug reservoirs, and have been utilized to direct drug at the target organ/tissue. Niosomes and liposomes are equiactive in drug delivery potential and both increase drug Efficacy as compared with that of free drug. Niosomes are preferred over liposomes because the former exhibit high chemical

stability and economy [8]. Niosome are useful in targeted drug delivery system& increased study in these structures gives various drug delivery system [9]. Amphiphiles other than natural phospholipids have been studied and found to form vesicular system similar to liposomes in physical characteristics. The other amphiphiles noted to form vesicles include saturated [10] and unsaturated fatty acids [11]. Niosomes are biodegradable, biocompatible & non immunogenic. It has been purposed and suggested that niosomes could be used an alternative version of liposomes to modify the Biodistribution and activity profile of drugs. Niosomes are formations of vesicles by hydrating mixture of cholesterol and nonionic surfactants[12]. These nonionic surfactants vesicles are called niosomes. Niosomal drug delivery has been studied using various methods of administration [13] including intramuscular [14], intravenous [15], peroral and transdermal [16,17]. In addition, as drug delivery vesicles, niosomes have been shown to enhance absorption of some drugs across cell membranes [18], to localize in targeted organs [19] and tissues and to elude the reticuloendothelial system. Niosomes has been used to encapsulate colchicines [20], estradiol [21], tretinoi [22,23], dithranol[24,25], enoxacin[26] and for application such as anticancer, anti-tubercular, anti-leishmanial, anti-inflammatory, hormonal drugs and oral vaccine[27-35]. Niosomes are helpful in solving various type of problem associated with drugs like instability, insolubility and rapid degradation of drugs. & this is also act as useful carrier for the hormones or bio active agents [36].

Advantage of niosomes

1. The vesicles may act as a depot, releasing the drug in a controlled manner.
2. Niosomal dispersion in an aqueous phase can be emulsified in a nonaqueous phase to regulate the delivery rate of drug and administer normal vesicle in external non-aqueous phase.
3. They are osmotic ally active and stable, as well as they increase the stability of entrapped drug.
4. Handling and storage of surfactants requires no special conditions.
5. They improve oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs.
6. They possess an infrastructure consisting of hydrophilic, amphiphiles and lipophilic moieties together and as a result can accommodate drug molecules with a wide range of solubilities.
7. The characteristics of the vesicle formulation are variable and controllable. Altering vesicle composition, size, lamellarity, tapped volume, surface charge and concentration can control the vesicle characteristics.
8. They improve the therapeutic performance of the drug molecules by delayed clearance from the circulation, protecting the drug from biological environment and restricting effects to target cells.

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Niosomes in Oncology

Niosomes containing anti-cancer drugs, if suitably designed, will be expected to accumulate within tumors in a similar manner to liposomes.

Methotrexate: Investigation carried out with methotrexate reveal that NSVs containing methotrexate exhibited an effect comparable to its liposomal counterpart. The distribution of methotrexate administered as NSVs was noticeably different as compared to MTX-Tween 80 in aqueous solution of methotrexate did not affect its distribution pharmacokinetics. Intravenous administration of methotrexate loaded noisome prepared from the same surfactants, did not lead to increased accumulation of the drug in the liver compared to administration of free drug. The study thus suggested that MTX contained in NSVs could be useful in maintaining the blood MTX level after Intravenous administration. Tumoricidal activity of niosomally-formulated methotreaxate is higher as compared to plain drug solution Incorporation of methotrexate in Span 60 and Span 85-cholesterol based NSVs has been reported. It was observed that span with increase lipophilicity their entrapment efficiency increased [37].

Doxorubicin

Tumoricidal activity was increased with different DOX niosome formulations as measured by decreased proliferation of the S-180 sarcoma in NMRI mice and terminal mean tumor weight of a MAC 15A tumor in NMRI mice. The surface of niosomes by incorporating polyethylene alkyl ether in the bilayered Structure. They compared the release pattern and plasma level of Doxorubucin in niosomes and Doxorubicin mixed with empty niosomes and observed a sustained and higher plasma level of doxorubicin from niosomes in mice. In a study DOX resistant ovary cell lining produced via repeated exposure to the agent and subsequently incubated with free and niosome entrapped DOX. It was observed that survival curve after niosomal DOX exhibited improved performance, however cross resistance was recorded. The use of doxorubicin a broad spectrum antineoplastic agent is hampered by a dose limiting cardiomyopathy and myelosuppresion. The altered levels of niosomal doxorubicin in Plasma along with the effect of encapsulation on metabolism. The clearance of doxorubicin released from niosomes was about 10nfold greater (176.5 ml/h) than the clearance of niosomal doxorubicin (16.2 ml/h). The area under the tumor level-time curve increased by over 50% as compared to plain drug solution [38].

Vincristine

Vincristine Span 40 niosomes increased the vincristine anti-tumour activity in S-180 sarcoma and Erlich ascites bearing mice. Span 60 bleomycin niosomes also increased the tumoricidal activity of bleomycin in these two tumour models [39]. Vincristine Niosomal formulation of vincristine exhibits higher tumoricidal efficacy as compared to plain drug formulation [40]. Also, niosomal formulation of carboplatin exhibits higher tumoricidal efficacy in S-180 lung carcinoma-bearing mice as compared to plan drug solution and also less bone marrow toxic effect [41].

Bleomycin

Niosomal formulation of bleomycin containing 47.5% cholesterol exhibits higher level drug in the liver, spleen and tumour as compared to plan drug solution in tumor bearing mice[42]. There is no significant difference in drug concentration with niosomal formulation in lung as compared to plan drug solution. Non Ionic Surfactant and oral drug delivery.

In the study of potential of Niosomal carrier system in oral drug delivery of

peptide drugs the absorption of 9-desglycinamide-8- arginine vasopressin (DGAVP) entrapped in $C_{12}EO_3$, $C_{12}EO_7$, $C_{18}EO_3$, and $C_{18}EO_7$ non-ionic surfactant based vesicles after oral administration was determined. The absorption studies were conducted *in vitro.* The stability of DGAVP was found to increase significantly in mucosal fluid on incorporation into niosomes[43]. Niosomal formulation of insulin prepared from span 20, 40, 60, 80 shows lower in-vitro release of insulin in simulated intestinal fluid from span 40 and 60 than span 20 and 80. Niosomes prepared from span 60 exhibits highest protection of insulin against proteolytic enzymes and good stability in presence of sodium deoxycholate and storage temperature [44].

Niosomes for the treatment of Leishmaniasis

Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, performed by Varshosaz et al., [45] showed high liver level after intravenous administration of the carriers forms of the drug. It is reported increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive[46].

Niosomes are as effective as liposomes in delivery of loaded drug in experimental leishmaniasis. The NSVs containing stilbogluconate tested in *vivo* recorded a spectrum of activity between 10 to 100 µg antimony per mouse. For drug with high aqueous solubility it was assumed that the drug is entrapped in aqueous space of the vesicles (liposomes or niosomes)[47]. NSVs prepared by ether injection method in which 450µmols of surfactant – Cholesterol (7:3) were dissolved in ether and NSVs were prepared by injecting the ethereal solution into 5ml of 300µg/ml aqueous solution of Stilbogluconate. The NSVs prepared were tested in Leishmaniasis donavani infected male BALB/c mice. It was found that in regard to the Biodistribution of stilbogluconate, the liposomes and niosomes were similar[48].

Niosomes as immunological adjuvant

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability[49]. Niosomes have been used for studying the nature of the immune response provoked by antigens. This is reported that niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability[50]. Hemoglobin containing niosomes were prepared and studied for functional a physical properties. Hemoglobin niosomes were prepared using Oreal's synthetic lipids by reverse phase evaporation method. The niosomes were unilamellar and were found to be permeable to oxygen, with hemoglobin dissolution profile modifiable quite closer to no encapsulated hemoglobin [51].

Diagnostic imaging with Niosomes

DTAP carrying niosomes (hexadecyl trglycerol ether: chol: DTAP 10:1:4) to study the *in vitro* release, radio labeling, in vivo distribution and to perform scintigraphic imaging studies[52]. Niosomes are considered as a carrier of iobitridol, a diagnostic agent for X-ray imaging. The noisome prepared using the film hydration method followed by sonication. Method allows the increasing encapsulation and the stability of vesicles were carried out [53]. Niosomal system

can be used as diagnostic agents. Conjugated niosomal formulation of gadobenate dimeglcemine with [N-palmitoyl-glucosamine (NPG)], PEG 4400, and both PEG and NPG exhibit significantly improved tumor targeting of an encapsulated paramagnetic agent assessed with MR imaging[54].

Anti-inflammatory agents

Diclofenac sodium noisome reportedly prepared from polysorbate 60, cholesterol and DCP (22:73:5) & 3 µ m in size were found to reduce the inflammation in rats with carrageen induced paw edema on intraperitoneal administration to a greater extent than the free drug. This increase in activity is a direct result of an observed increase in the area under the plasma time curve [55]. Niosomal formulation of Nimesulide and flurbiprofen also exhibits greater anti-inflammation activity as compared to free drug [56, 57]. Niosome of Sumatriptan succinate was prepared using lipid hydration method. The prepared niosomes were evaluated for entrapment efficiency, size analysis and *in vitro* release studies. Further niosomes were evaluated for nasal absorption using an ex-vivo model. The niosome reported to enhance the drug absorption & prolongation [58].

Transdermal delivery of drugs by niosomes

An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. It has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse [59]. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands. Niosomes have also been used to encapsulate lidocaine [60], estradiol [61], cyclosporine [62], erythromycin, alpha interferon [63] for topical and transdermal delivery.

In Oestradiol *in vitro* transdermal studies $C_{12}EO_7$ niosomes are better transdermal carrier. The higher flexibility of these bilayers is said to be responsible for this improved transdermal penetration. & reducing the cholesterol content of these niosome also increase the transdermal delivery of oestradiol [64].

The migration of Cyclosporine A from cyclosporine glyceryl dilaurate /$C_{16}EO_{10}$/cholesterol niosomes into deeper strata has also been studied *in vitro* and it was found that the factor such as dosing volumes produced an increased uptake of the drug into deeper skin strata. It shows niosomes appears promising for both hydrophobic and amphiphiles drug.

Drug delivery through niosomes is one of the approaches to achieve localized drug action, since their size and low penetrability through epithelium and connective tissue keeps the drug localized at the site of administration. Localized drug action results in enhancement of efficacy of potency of the drug and at the same time reduce its systemic toxic effects. The evolution of niosomal drug delivery technology is still at an infancy stage, but this type of drug delivery system has shown promise in cancer chemotherapy and antileishmanial therapy.

Conclusion

Niosomes drug delivery systems have played a significant role in for improve their therapeutics of drug. Niosomes represent promising drug delivery systems. They present a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure.

Niosomes are thought to be better candidate's drug delivery as compared to liposomes due to various factors like cost, stability. Also niosomes have great drug delivery potential for targeted delivery of anti-cancer, anti-infective agents. Anti-inflammatory agents, transdermal drug delivery, fairly recently as vaccine adjuvant and as diagnostic imaging agents.

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