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Review Article

Niosomes as Nano-carrier Based Targeted Drug Delivery System

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Abstract

Niosomes are considered as novel nano-carrier in the drug delivery systems. These are much more stable than other nano-carriers like liposomes and nanoparticles. It is an example for targeted and control release of medication. The drug is entrapped into lipid core so that it prevents the drug from leaching. Here the drug will be targeted only to the desired cell/tissue and not to the non-targeted cells. By giving this formulation we can thereby reduce the dose of the drug and toxicity. This review article mainly emphasizes on the potential applications of niosomes in targeted drug delivery system.

Keywords: niosomes, nanocarriers, targeted drug delivery.

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INTRODUCTION

Niosomes are formation of vesicles prepared by the mixing of cholesterol and a non-ionic surfactant. It is an example for targeted and controlled release of medicament. There are various approaches for delivering these drugs like liposomes, niosomes, nanoparticles etc. Niosomes are preferred over liposomes because the former exhibit much more stability and economic. They enhance the therapeutic efficacy of the drug molecules by delaying the clearance from the circulation and protecting from environment. Niosomes are widely used for targeted drug delivery system¹. Paul Ehrlich in 1990 started the era of targeted drug delivery systems. The major mechanism is that the drug will be targeted only to its site of action and not to the non-targeted cells. Hereby we can reduce the toxicity. The formulation of niosomes consists of non-ionic surfactants eg. span 60 along with cholesterol is added in order to attain the stability of formulation.

ADVANTAGES

- The characteristics features like size, shape, nature can be changed.
- Enhances the stability of the entrapped drug.
- Improves the penetration of drug into the skin.
- They are osmotically active hence has longer storing period.
- The vesicles act as a transporter for the slow release of medication in a controlled manner.
- Better patient compliance².

DISADVANTAGES

- Leaching of drug may occur.
- Difficult method of preparation.
- Aggregation or fusion.
- Stability issues.

STRUCTURE OF NIOSOMES:

It includes 3 major components:

1. Non-ionic surfactants.
2. Cholesterol.
3. Charge inducing molecule³.

Non-ionic surfactant: These have no charged groups in their structure. These are much more stable, biocompatible and less toxic than anionic, amphoteric and cationic surfactants. Non-ionic surfactants are amphiphilic molecules that include two different regions: one of them is hydrophilic (water-soluble) and the other one is hydrophobic (organic soluble).

Eg: spans 20,40,60 tween 20,40,80

Cholesterol: Cholesterol helps in the formation of hydrogen bonds with hydrophilic head of surfactant. The amount of cholesterol in the formulation influences the stability of the niosome. Cholesterol enhances the rigidity of the vesicles.

Drug entrapment efficiency can be altered by using various concentration of cholesterol.

Charge inducing molecule: The presence of a charge inducing molecule enhances the stability of the niosome formulation. Diacetyl phosphate and phosphatidic acid are commonly used to induce negative charge to the niosome formulation similarly stearylamine is used to induce positive charge to the formulation. The concentration must be 2.5-5 mol%.

CLASSIFICATION OF NIOSOMES:

- Small unilamellar vesicle 0.025-0.05 μ m.
- Large unilamellar vesicle $\geq 0.05\mu$ m.
- Multi lamellar vesicle $\geq 0.10\mu$ m⁴.

METHOD OF PREPARATION:

General Method of Preparation⁵:

1. Thin Film Hydration Technique (Hand shaking method)

2. Ethanol Injection Method:

Various other methods can also be used for the Preparation of niosomes:

- Sonication method
- Multiple Membrane extrusion method.
- Micro fluidization
- Reverse phase evaporation
- Bubble method
- Tran's membrane pH gradient Drug Uptake Process method

APPLICATION OF NIOSOMES

Niosomes as drug delivery systems: The fundamental purpose of a targeted drug delivery system is to increase the selectivity towards the targeted tissue and also to reduce the toxicity of the medication. In 1909 Paul Ehrlich developed a drug delivery system that can directly target the drug to a diseased cells and tissues. Various systems such as Immunoglobulins, liposomes, microspheres and Niosomes

were used as a vehicle for the drug to the target cells and tissues. Among these, liposomes and niosomes obtained special consideration due to its unique properties and stability features. Niosomes have the ability to entrap both hydrophilic and lipophilic drugs. Presence of non-ionic surfactant and the lipid makes niosomes a better carrier of drug(s) to tumor, liver and brain. They are widely used nowadays in targeting of the drug for treating cancers, parasitic, viral and other microbial diseases more effectively ⁶.

Aerosolized Niosomes with anti-cancer potential:

Gemcitabine and cisplatin loaded aerosolized niosomes was synthesized for the treatment of lung cancer. Cytotoxicity study of formulation against normal lung (MRC5) and lung cancer (A549) cell lines was investigated. The results revealed that the optimized formulation had reduced cytotoxicity against both MRC5 and A549 cell lines when compared with the control system (Gem + Cis alone) from highly toxic ($IC_{50} < 1.56 \mu\text{g/mL}$) to weakly toxic ($IC_{50} 280.00 \mu\text{g/mL}$) and fairly toxic ($IC_{50} = 46.00 \mu\text{g/mL}$), respectively, after 72 h of treatment. These findings promised that the optimized aerosolized niosomal formulation has excellent anti-tumor activity and can be used as promising drug delivery system ⁷.

Niosomes improved the bioavailability of atorvastatin calcium:

Atorvastatin calcium is an HMG-CoA reductase inhibitor. The oral bioavailability is less than 12%. The drug is highly soluble in acidic pH and is absorbed in upper GIT. Therefore, to compensate these problems atorvastatin calcium has been formulated in the form of niosomes. The niosomes were prepared using thin film hydration technique using different grades of surfactants like span 40, span 60 and span 80. The characterization studies were performed and evaluated for its shape, size and entrapment efficiency. The study proved that atorvastatin calcium niosomes has improved the oral bioavailability and stability of the formulation proving to be one of the promising and fundamental nanocarrier ⁸.

Methylene Blue loaded niosomes with wound healing:

Methylene Blue (MB) loaded niosomes were prepared by using the ultra-sonication method as a green formulation method. The prepared niosomal formulation were optimized by using Behnken design. Characterization studies were performed to evaluate the vesicle shape, drug entrapment efficiency and zeta potential. The drug entrapment efficiency of the formulation was increased. Male Wistar rat was used to study the In vivo efficiency of enhanced formulation. The levels of Superoxide dismutase (SOD) and malondialdehyde in the skin sample were evaluated which can cause tissue damage and delay in wound healing ⁹.

Levofloxacin loaded niosomes with anti-bacterial:

Levofloxacin entrapped niosomes were prepared and examined the effectiveness in treating *Pseudomonas aeruginosa* infections in Dawlwy rats. Thin film hydration method is used to develop the niosomes and then niosomes was assessed for in vitro drug release and stability. Studies were conducted by using drug free niosomes, Drug loaded niosomes and free drug and blood samples were collected. The results revealed that the niosome treated group significantly reduced complete blood counts and viable bacterial counts (CFU) in the liver, kidney, and spleen ¹⁰.

D-limonene-loaded niosomes with cytotoxic activity:

D-limonene-loaded niosomes (D-limonene/Nio) was developed for tumor therapy. The niosomal formulation was synthesized by conventional thin film hydration technique with Span® 40: Tween® 40: cholesterol (35:35:30 molar ratio) and characterized. The entrapment efficiency of the

formulation was found to be about $87 \pm 1.8\%$. Prolonged release of D-limonene was observed from prepared niosomes when compared to free D-limonene. The cytotoxicity study results revealed that the prepared niosomes increase the cytotoxic activity with all three cancer cell lines (HepG2, Macf-7 and A549) at the concentration of $20 \mu\text{M}$ ¹¹.

Mirtazapine loaded niosomes - improved bioavailability:

mirtazapine loaded niosomes was synthesized for nasal drug delivery. Mirtazapine is an anti-depressant drug with poor oral bioavailability. Therefore, the drug has been formulated in the form of niosomes mainly to improve the bioavailability. Niosomes was formulated by using thin film hydration technique and optimized using 3^2 full factorial design. Mirtazapine loaded niosomes was then fused into a Poloxamer 407 and Carbopol 934 in-situ gel. The study revealed that niosomal in-situ gel of Mirtazapine can be used for a prolonged period by minimizing drug administration frequency and thus improves the bioavailability ¹².

Quercetin loaded niosomes - improved solubility:

flavonoid loaded niosomes was prepared to improve its solubility, stability and penetration ability. Whitening and antioxidant Properties of several flavonoids were studied, including quercetin, morin, myricetin, rutin, and breviscapine. The drug loaded niosomes were characterized and entrapment efficiency was determined. The photostability, solubility, release behavior, ex vivo drug penetration, and skin retention properties of Niosome preparation were studied. Drug entrapment efficiency of quercetin loaded niosomes was found to be high. The niosome preparation remarkably enhanced the solubility and photo-stability of drug quercetin ¹³.

Temozolomide loaded niosomes - Brain drug delivery:

Temozolomide incorporated niosomes was used for the treatment of glioblastoma, a destructive brain tumor. The prepared niosomes are then surface modified with chlorotoxin, which is a small 36 amino acid peptide. It will produce an increase in the accumulation of drugs in the cerebri of brain by active targeting mechanism. Temozolomide-loaded niosomes were developed using thin-film hydration method and then characterized. Quantitative tissue distribution studies revealed that enhanced permeation of the medication into the brain was achieved by the niosome formulation ¹⁴.

Glipizide-loaded Niosomes - improved bioavailability:

Glipizide-loaded Niosomes was formulated to enhance the oral bioavailability of the drug. Highest percentage of drug entrapment was observed in the optimization process. The in vitro drug release studies from Niosomes showed a prolonged drug release for more than 24 h. Zeta potential value is found to be negative which reveals that Glipizide Niosomes were stabilized by electrostatic repulsive forces. Maximum entrapment and suitable drug release rate are observed for invitro evaluation of the Glipizide niosomes. Niosomal formulation of glipizide is found to improve the bioavailability and prolonged drug release profile ¹⁵.

Carum loaded niosomes-anticancer activity:

Carum-loaded niosomes was prepared and evaluated on breast cancer cells. Thymoquinone (TQ), a phytochemical compound found in carum seeds (C.carvil) was the drug used. In this study, they introduced an innovative niosome delivery system with ergosterol (herbal liquid) in structure, instead of cholesterol. It resulted in high stability, nanometric size, good encapsulation efficiency niosomes. In this study they evaluated properties of TQ, TQ loaded niosomes, carum and carum loaded niosomes and their efficiency was compared on the breast cancer cells ¹⁶.

Pegylated niosomal with albendazole - anti-fungal activity: Pegylated niosomal formulation of albendazole was developed for the treatment of echinococcosis. The main purpose of the study is to enhance the systemic residence time of the albendazole which would help in the treatment of echinococcosis. Niosomes were synthesized by using ethanol injection method and characterization studies were conducted to evaluate morphological size, shape, and in vitro release study. The results concluded that the niosomal formulation has the ability to use in the treatment of echinococcosis and hydatid cysts.¹⁷

Cisplatin loaded niosomes-anticancer activity against Breast cancer cells: In this study they prepared nanoniosomated cisplatin and evaluated its efficacy in the BT-20 cell line *in vitro*. Niosome containing cisplatin were synthesized by reverse-phase evaporation method and characterized. Further studies revealed that the niosomes increased the cytotoxic effects of cisplatin by 1.5 times than the standard drug. The study confirms that niosomes prove to be a promising nanocarrier for cisplatin.¹⁸

Herbal drug loaded niosomes: Herbal drug loaded niosomes were prepared as topical gel for transdermal drug delivery. Niosomes were synthesized by using thin film hydration technique. The herbal drug was successfully loaded in the niosomes using span 20, 60, 80 and cholesterol. The prepared niosomes were assessed for their particle size, morphology and in vitro drug release and the optimized formulation (batch 7) shows highest drug entrapment efficiency. Plain herbal gel and niosomal herbal gel were compared for their in vitro drug release properties and niosomal gel preparation gives better results.¹⁹

Curcumin loaded niosomes -anticancer activity against ovarian cancer cells: Curcumin loaded niosomes, its characterization and cytotoxic effect on ovarian cancer cells was studied. Curcumin is a poorly water-soluble drug with rapid degradation. Hence it has been formulated in the form of niosomes in order to compensate these disadvantages. Curcumin has been encapsulated into the niosome core using non-ionic surfactants like span 60 and tween 80. Entrapment efficiency was increased. Curcumin niosomes proved to improve the cytotoxic activity and apoptotic rate against ovarian cancer.²⁰

Artemisone loaded niosomes- skin anticancer activity: Artemisone is a 10-amino-artemisinin moiety, having antimalarial property along with anticancer activity. In this study they developed artemisone loaded niosomes using thin-film hydration technique. Cytotoxicity study results show high selectivity towards the tumor cells with inconsequential toxicity towards the normal skin cells. The artemisone loaded niosomes completely inhibited melanoma cells than the free artemisone drug.²¹

Benzoyl peroxide loaded niosomal gel - Anti-bacterial activity: Benzoyl peroxide loaded niosomal gel was synthesized for its topical delivery in to the skin. The main aim of the study was to improve the drug permeation through the skin. Later the niosomes were further loaded in the carbopol gel to increase the contact time of the gel. The study revealed that the prepared niosomal gels have the ability to improve the drug permeation through the skin. After four days of treatment the niosomal gel reduced the bacterial infection. The study concluded that niosome formulation has got much more advantages than other conventional dosage forms.²²

Diclofenac sodium loaded niosomes: Diclofenac sodium multilamellar vesicle (MLVs) was formulated using thin film hydration method. Cholesterol and surfactant (span 60)

were used in different ratio for the preparation. In vitro drug release from the preparation was found to be consistent and a stability study was conducted to in order to learn the ability of drug to be leached out from the formulation upon storage at room temperature $25 \pm 20^\circ\text{C}$ as well as in refrigerated condition (20°C to 80°C). The considerable stability of niosomal formulation was found to be 2 weeks. In short encapsulation of diclofenac sodium in the niosomal suspension was found to be increased when compared to the conventional drug.²³

Tenofovir disoproxil fumarate loaded niosomes - improved bioavailability: Tenofovir disoproxil fumarate (TDF) niosomes have been prepared with the aim of improving the oral bioavailability of which is an anti-HIV drug. Thin film hydration technique was used. Different concentration of surfactant, cholesterol, and dicetyl phosphate were used to formulate the niosomes. Niosomes prepared with 1:1:0.1 ratios of surfactant: cholesterol: dicetyl phosphate with each grade of span shows higher entrapment efficiencies. Maximum drug release (99.091%) is obtained for the niosomes prepared with sorbitan monostearate with zero order rate kinetics. In vivo study results revealed that the prepared niosomes significantly improve the oral bioavailability of TDF after the dose of 95mg/kg in rats. By using TDF loaded niosome more than two-fold enhancement in the oral bioavailability of the drug is observed.²⁴

Itraconazole loaded niosomes- anti-fungal activity: Itraconazole loaded niosomes were formulated and evaluated for anti-fungal activity. Factorial design is used to optimize the Surfactant: cholesterol ratio and quantity of ethanol used in the formulation was studied. Vesicle size, entrapment efficiency, drug release, skin permeation, and antimycotic activity of the prepared niosomes were studied. Further study results revealed that Itraconazole niosome has much more inhibitory action than the marketed formulation against *C. albicans*.²⁵

Isoniazid loaded niosomes-anti-tuberculosis activity: Isoniazid loaded niosomes were synthesized by using reverse phase evaporation method, which was used for the treatment of tuberculosis. The surfactants used were span 60 and span 20. A charge inducing agent like di-acetyl phosphate was added. Characterization studies were conducted in order to determine the zeta potential, particle size and poly dispersibility index. The study revealed that isoniazid formulations have reduced dose and toxicity when given parenterally or by any other routes.²⁶

Cantharidin loaded niosomes-anticancer activity against breast cancer cells: Cantharidin loaded niosomes were synthesized by using injection method. The ability in intensifying the antineoplastic activities of the drug and decreasing its toxicity was studied on human breast cancer cell line MCF-7. The in vivo therapeutic efficacy of the preparation was examined in S180 tumor-bearing mice. 1.0mg/kg niosomal-cantharidin formulation was administered into mice, showed most effective antitumor activity, with an inhibition rate of 52.76%. The activity of the formulation found to be significantly higher than that of concentration of free cantharidin.²⁷

Tamoxifen citrate loaded niosomes-anticancer activity against breast cancer cells: Tamoxifen citrate loaded niosomes were synthesized by conventional thin film hydration technique for the treatment of human breast cancer. The niosomal formulation of tamoxifen was optimized and showed considerably increase in cellular uptake (2.8-fold) and exhibited appreciably larger anti-cancer activity on MCF-7 breast cancer cell line. Niosomal

tamoxifen showed improved tumor volume reduction when compared to free tamoxifen ²⁸.

Doxorubicin loaded niosome-anticancer activity against breast cancer cells: An effective tumor-targeted niosome drug delivery system was intended and developed. Niosomes were synthesized by using a combination of surfactant (Pluronic L64) and cholesterol. The drug doxorubicin was loaded into the niosome, then transferrin was conjugated to niosomes surface. They have studied the anticancer activity against MCF-7 and MDA-MB-231 tumor cell lines. A markable decrease in viability is observed ²⁹.

CONCLUSION

Niosomes as nano-carrier can be used for targeted drug delivery system. niosome formulation has been reported as stable formulation and anti-cancer drugs, anti-bacterial drugs, anti-inflammatory drugs, anti-viral drugs can be encapsulated. Niosomes can be used as promising drug nano-carriers to achieve better bioavailability and targeting approaches. Thus, niosomes drug delivery requires further research on correlation of *in vivo* and *in vitro* study results. So, this will bring out the niosome formulation as a promising targeted drug delivery module.

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