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A REVIEW: NIOSOMES A NOVEL TOOL FOR DRUG DELIVERY

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Abstract

There are two important requirements in design and development of novel drug delivery system(NDDS).First it should deliver the drug at pre-determined rate and second therapeutic effective amount of drug should reach the site of action. The conventional dosage forms like tablets, capsules are unable to meet this requirement. Noisome are nonionic surfactants vesicles formed due to self-assembly of hydrates surfactant monomers. The proposed review deals with the composition, methods of preparation, stability, therapeutic potential. Mainaim for development of noisome is for sustain release of the drug and for drug targeting to specific sites of the body.

Keywords:

Composition, Methods of preparation, Stability, Therapeutic potentials.

Introduction

Recently, considerably attention has been given to new drug delivery systems. The NDDS should ideally fulfill two requirements. First, it should deliver the drug at pre-determined rate and second therapeuticeffective amount of drug should reach the site of action[1].Noisome are nonionic surfactant vesicles in aqueous media resulting in closed bilayer structures that can be used as carriers of amphiphillic and lipophilic drugs [2].Noisome are unilamellar or multilamellar vesicles in which an aqueous solution of solutes are entirely enclosed by a membrane formed due to organization of surfactant macromolecule as bilayer. Niosomes are formed due to hydration of nonionic surfactant film which hydrates eventually to encapsulate the hydrating aqueous solution[3].The synthetic nonionic surfactant which are used for the preparation of noisome are stable chemically with utmost accurate chemical composition and cheaper in cost. Niosomes

are analogues of liposomes and widely used experimentally as drug carrier and in cosmetic formulations.Niosomes were firstly introduced by Handjani Vile *et al* in 1979 [4].

Various advantages and disadvantages of niosomes are reported in the table given below: [5, 6] Table 1.

Table1: Advantages and Limitations of Niosomes

ADVANTAGES	LIMITATIONS
1. Bioavailbility of poorly absorbed oral drug and skin penetration of drugs is enhanced.	Physical instability is observed in niosomal formulations due to vesicles aggregations, fusion and leaking thereby leading the hydrolysis of encapsulated drug which affects the shelf life of the prepared dispersion.
2.High patient compliance in comparison with oily dosage forms as the vesicle Suspension is a water–based vehicle.	NA
3. Drug molecules with a wide range of solubility's can be incorporated.	NA
4. Characteristics of vesicle formed are variable and controllable. Vesicle characterization can be controlled by composition , size ,lamellar surface charge and concentration.	NA
5. Vesicles act as a depot thereby releasing the drug in controlled manner.	NA
6.Osmotically active, stable, as well as they enhance the stability of entrapped drug.	NA
7. It can be formulated to reach the site of action by oral, tropical, as well as parenteral routes.	NA
8. No specific condition is required for storage and handling of various surfactants.	NA
9. Surfactants used for formulation of niosomes are biocompatible, non-immunogenic and biodegradable.	NA

Niosomes Composition

Theoretically, for the formation of niosomes presence of a particular amphiphile and aqueous solvent are required. Due to high interfacial tension between water and hydrocarbon portion the association of amphiphile monomers into vesicle occurs due to hydration. Simultaneously,ionic and steric hydrophilic repulsion between the head groups ensure that this group remains in contact with water.Hence,the two opposite forces leads to supramolecular assembly. The essentialcomponents in the preparation of niosomesare membrane additives such as cholesteroland non-ionic surfactants.

Cholesterol

Cholesterol is a waxy steroid metabolite foundin the cell membranes. Cholesterol is addedusually to the non-ionic surfactants to giverigidity and orientational order to the niosomalbilayer [7]. Cholesterol and its derivatives are themost common additives found in niosomalsystems. Cholesterol enables the formation ofvesicles, reduces aggregation and providesgreater stability. Cholesterol is also known toabolish gel to liquid phase transition ofniosomal systems resulting in niosomes thattare less leaky [8].

Non-ionic surfactants

The main component for niosomal formations is non-ionic surfactant. Generally, they possess hydrophilic head group and a hydrophobic tail. The hydrophobic moiety may be made up of 1/2/3 alkyl chains or single stearyl group or perfluro group. The length of alkyl chain is from C_{12}- $C_{18.}$ The chain length of per fluro alkyl group is $C_{10.}$ The commonly used surfactant in literature is Sorbitan fatty acid esters and commonly used Spans are Span 20, 40,60,65,80, and 85. Tweens are also employed as non-ionic surfactants for the formation of niosomes and example of generally employed Tweens are Tween 20, 40 and 60.Tweens ispolysorbates

derived from PEGylated sorbitan esterified with fatty acids [9]. Solulan C24 poly-24-oxyethelene cholesterylether has been reported to form spherical,tubular or polyhedral niosomal vesicles [10].Another class of non-ionic surfactants ispolyoxyethylene alkyl ethers (CnEOm , Brij TM)which have ability to form bilayer vesicleswhen mixed with cholesterol. The differentgrades of Brij used for vesicle formation areBrij 30, 35, 52, 58, 72, 76, 92, and 97.Numerous studies have been reported inliterature using these surfactants [11]. Crown ether units, as polar heads, linkedto a long alkyl chain and represent a new classof non-ionic surfactants, which are able toassemble in colloidal structures if associated withcholesterol [12].Table 2 describes the summary of surfactants used for preparation of niosomes.

Table 2: Summary of surfactants used for preparation of Niosomes.

S.No.	Name of surfactant	HBL Value	Trademark
1.	Sorbitan monostearate	4.7	Span 60
2.	Sorbitan monopalmitate	6.7	Span 40
3.	Sorbitan monolaurate	8.6	Span 20
4.	Sorbitan trioleate	1.8	Span 85
5.	Sorbitan monooleate	4.3	Span 80
6.	Polyoxyethylene (20) sorbitan monolaurate	16.7	Tween 20
7.	Polyoxyethylene sorbitan monopalmetate	15.6	Tween 40
8.	Polyoxyethylene sorbitan monostearate	15.6	Tween 60
9.	Polyoxyethylene sorbitan monooleate	15.5	Tween 80
10.	Polyoxyethylene laural ether	9.5	Brij 30
11.	Polyoxyethylene 23 laural ether	16.9	Brij 35
12.	Polyoxyethylene 2 cetyle ether	16.9	Brij 52
13.	Polyoxyethylene 20 cetyle ether	15.7	Brij 58
14.	Polyoxyethylene 2 stearyle ether	4.9	Brij 72
15.	Polyoxyethylene 10 stearyl ether	12.4	Brij 76
16.	Polyoxyethylene 2 oleyl ether	4.9	Brij 92

Other additives

Charge inducers are one of the membraneadditives which are often included in niosomesbecause they increase surface charge densityand prevent vesicles flocculation, aggregationand fusion. Negatively and positively charged molecules are used for induction of charge inniosomes as reported by number of scientists.Dicetyl phosphate (DCP) and stearyl amine (SA) which induces negative or positivecharge is examples of such membrane.

Additives.

Methods of Preparation

The general method for the preparation of Niosomes includes the evaporation of the solvent to produce a lipid film followed by hydration with the hydration medium. However,various methods are utilized for the preparation of niosomes. Some of them are discussed below:

Ether injection method

This method was reported in 1976 by Deamerand Bangham. It is similar to ethanol injectionmethod. However it differs with ethanolinjection method in many ways. It involvesinjection of immiscible organic solutioncontaining surfactant or surfactant-cholesterolor surfactant cholesterol-diacetyl phosphate orsurfactant cholesterol- drug solution mixturevery slowly into an aqueous phase through anarrow needle at vaporization temperature oforganic solvent. Vaporization of

ether leads tothe formation of single layered vesicles(SLVs). It has a little risk of causing oxidativedegradation provided ether is free fromperoxides. The disadvantage of this method isthat a small amount of ether is often present inthe vesicles suspension and is difficult toremove very often [13].

Ethanol injection method:

This method has been reported as one of thealternatives used for the preparation of smallunilamellar vesicles (SUVs) without sonication.In this method, an ethanol solution ofsurfactant is injected rapidly through a fineneedle into excess of saline or other aqueousmedium. Vaporization of ethanol leads to theformation of vesicles. Enoxacin was entrappedin niosomes using this particular method[14].

Hand shaking method (Lipid film hydration)

In this method, surfactants/lipids are casted aslayers of film from their organic solution usingflask rotary evaporator under reducedpressure (or by hand shaking) and then castedfilms are dispersed in an aqueous medium.Upon hydration, the lipids swell and peel offfrom the wall of the round bottom flask attemperature slightly above the phase transitiontemperature of surfactants used, for specifiedperiod of time (time of hydration) with constantmild shaking. The mechanical energy requiredfor the swelling of the lipids and dispersion ofcasted lipid film is imparted by manualagitation (hand shaking) or by exposing thefilm to a stream of water saturated nitrogen for15 minutes followed by swelling in aqueousmedium without shaking (non shakenvesicles). Hand shaking method producesmulti lamellar vesicles (MLVs) while vesiclesproduced by non shaking method are largeunilamellar vesicles LUVs[15].

Reverse phase evaporation:

The novel key in this method is the removal ofsolvent from an emulsion by evaporation. Thesurfactant and cholesterol are dissolved inether or chloroform or in a mixture ofchloroform and ether chloroform with orwithout drug. The resulting two-phase systemis then homogenized using homogenizer. Theorganic phase is removed under reducedpressure to form niosomes dispersed inaqueous phase. In some cases, resultingsuspensions must be further hydrated orhomogenized to yield niosomes[16].

The Bubble method:

It is novel technique forone step preparation of liposomes andniosomes without the use of organic solvents.The bubbling unit consists of round-bottomedflask with three necks positioned in water bathto control the temperature. Water-cooled

refluxand thermometer is positioned in the first andsecond neck and nitrogen is supplied throughthe third neck. Researchers dispersedcholesterol and surfactants together in buffer(pH 7.4) at 70°C, the dispersion is mixed for15 seconds with high shear homogenizer andimmediately afterwards "bubbled" at 70°Cusing nitrogen gas[17].

Microfludisation

This is a recent technique to prepare smallmulti lamellar vesicles. A microfludizer is usedto pump the fluid at a very high pressure(10,000 psi) through a 5 pm screen.Thereafter; it is forced along defined microchannels, which direct two streams of fluid tocollide together at right angles, therebyaffecting a very efficient transfer of energy.The lipids can be introduced into the fluidizer.The fluid collected can be recycled through thepump until vesicles of spherical dimensionsare obtained. This method resulted inniosomes with greater uniformity afford smallsize which shows better reproducibility [18].

Multiple membrane extrusion method:

Inmembrane extrusion method, the size ofniosomes is reduced by passing them throughmembrane filter. This method can be used forproduction of multi lamellar vesicles as well aslarge unilamellar vesicles. It is found as a goodmethod for controlling niosomal size[19].

Stability of Niosomes

Stability in buffer: Stability of alkyl glycoside vesicles was compared with phosphatidylcholine based liposomes vesicles both containing lipid: DCP: cholesterol 4:1:2. It was observed that the phosphotidylcholine based vesicles(liposomes) disintegrated *in vitro* after 22 week while niosomes prepared using alkylglycoside endured at least for 25 weeks.[20].Comparison with the efflux profile it was observes to be biphasic.

Stability in hypertonic media (Osmotic Shrinkage):

Addition of hypertonic salt solution to the suspension brings osmotic gradient acrossnon ionicsurfactant (NSV's).Higher absorbance has been recorded in hypertonic buffer.[21].It was interpreted that the osmotic gradient induces the reduction in vesicle size by effectively pumping out the vesicular contents.

Stability in hypotonic media:

Unlike, osmotic shrinkage the vesicular system containing high load of solutes wen diluted with demineralized water, a slow release of drug for 1hr period followed by relatively faster drug release phase in water was observed.[3]

Theurapeutic Potentials

Niosomes for the therapeutic of Leishmaniasis: The stability characteristics of niosomes with appropriate release profile can be prepared by incorporating surfactant chemically or via modification in the bilayer composition.But real therapeuticpotential can only be evaluated by *in vivo* experiments in animals along with the clinical trials.

NSV's prepared using surfactant I-III have been recorded to be effective carrier system for delivery of stilbogluconate to the visceral cells.[22]An exhaustive review on liposomal vesicular system in parasitic disease reported that the magnitude of improved efficiency is also dependent on the experimental conditions [23].It include variables such as size of the host, route of administration , volume , time profile.Niosomes are as effective as liposomes in delivery of loaded drug in experimental Leishmaniasis[24].NSV's so prepared were found to be effective in the treatment of Leishmaniasis.

Niosomes in Oncology

Dixorubicin (DOX) based niosomes were formulated and evaluated where surfactant I: Cholestrol (50:50 molar) was used as basic vesicular components. The prepared formula was administered as bolus through tail caudal vein at a dose of 5mg per kg body weight.The drug was estimated in serum, liver, heart, lungs and tumor after administration of the drug .It was found to distribute rapidly after I.V administration. The plasma doxorubicin levels were higher for entire periodof study confirming sustained release characteristic of niosomal preparation.[25].

Higher DOX tumor concentration showed an improved antitumor activity. Study suggested that administration of NSV's –DOX increased life span of tumor bearing mice and regressed the tumor. When methotrexate is incorporated in Span 85 and Span 60 cholesterol based NSV's.It was observed that in Span(s) with increased lipophilicity their entrapment efficiency also increased [25].Adrimycin loaded niosomes using monoalkyltriglycerol ether were prepared and tumouricidal activity was compared against free drug.[26].

Cosmetic delivery:

The first report of non-ionic surfactant vesicles came from the cosmetic applications devised by L'Oreal. Niosomes were developed and patented by L'Oréal in the 1970s and 80s. The first product 'Niosome' was introduced in 1987 by Lancôme. The advantages of using niosomes in cosmetic and skin care applications include their ability to increase the stability of entrapped drugs, improved bioavailability of poorly absorbed ingredients and enhanced skin penetration [27].

Vaccine delivery

An interesting group of vaccine carriersystems are formulations based on non-ionicsurfactant vesicles (niosomes) whichthemselves are only weekly immunogenic.Niosomes are gaining wide attention asperoral vaccine delivery system and for topicalimmunization. Non-ionic surfactant vesicles ofinfluenza antigen for nasal mucosal deliverywere studied. The study described theencapsulation of viral influenza vaccineantigen in non-ionic surfactant vesicles usingdehydration-rehydration technique. Influenceof the varying proportion of surfactant,cholesterol, and dicetyl phosphate on themorphology, particle size, entrapmentefficiency, and *in-vitro* antigen release fromniosomes was investigated. The stability of theantigen was studied using sodium dodecylsulphate (SDS)-polyacrylamide gelelectrophoresis and immunoblotting.Researchers also studied the effect ofcholesterol concentration and the method oflyophilization on antigen loading and *in-vitro*release of antigen from surfactant vesicles [28]. Niosomes for topical DNA delivery of HepatitisB surface antigen (HBsAg) were prepared byreverse phase evaporation method using Span85 and cholesterol. The immune stimulatingactivity was investigated and it was observedthat topical niosomes elicited a comparableserum antibody titer and endogenouscytokines levels as compared to intramuscularrecombinant HBsAg and topical liposomes [29].

Conclusions and Future Potential

Niosomes are new and latest drug delivery system which has been getting attention from early 1990's. For its exploitation and investigation it holds great value and promising results can be achieved. It offers great opportunity in various drug delivery systems as the structural modification can be achieved like its shape, size, lamellar nature and the type of composition to be used while preparing niosomes.

It's an innovative way to incorporate the molecule by altering the solubility, permeability and toxicity problems associated with respective drug molecule.

It has been observed that higher stability is achieved in comparison to liposomes as it has the ability to incorporate both hydrophilic and hydrophobic molecule. With several administration route available makes niosomal drug delivery more reliable and promising.

By analyzing the relative new data and existing data indicatethe future of niosomes is very bright.

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