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Review Article

Niosomes: A Novel Carrier for Drug Delivery

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Abstract

Colloidal drug delivery systems such as liposomes and niosomes have distinct advantages over conventional dosage forms. These systems can act as drug reservoirs and provide controlled release of the active substance. Basically, these vesicles do not form spontaneously. The mechanism of vesicle formation upon use of nonionic surfactants is not completely clear. The most common theory is that nonionic surfactants form a closed bilayer in aqueous media. Formation of this structure involves some input of energy, for instance by means of physical agitation or heat. In this review the preparation, evaluation and applications of niosomal drug delivery system was discussed

Key words: entrapment efficiency; drug content; drug release; surfactant; cholesterol

Introduction

Paul Ehrlich in 1906, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target drugs directly to diseased cells.

Drugs incorporated in liposomes, niosomes are not activated under physiological conditions and do not cause unfavorable side effects as well [1].

There are various techniques by which drug can be targeted include.

1. Nanoparticles

2. Niosome

3. Resealed erythrocytes

4. Microspheres

5. Monoclonal antibodies

Niosomes

Non ionic surfactant vesicle is a best alternative to phospholipids vesicle. Vesicles are closed bilayer structure prepared by self assembly of amphihiles by means of aqueous media. Physical agitation and heat act as source of energy in vesicles preparation. Hydrophilic molecules trapped in aqueous core and lipophilic molecules entrapped in lipids bilayer [2].

Advantages of Niosomes:

Non ionic surfactant vesicle is one of the best nano-carrier having lot of advantages like

- Niosome contain hydrophilic and hydrophobic domain so it can provide

loadings of API with diverse solubility.

- Surfactant vesicles improve penetration of molecule through skin.
- Drug molecule entrapped in vesicle bilayer or aqueous core, so API diffuse

through vesicle in sustained manner

- Vesicles are non toxic because of it degradable in natural way &

compatible.

- Therapeutic efficiency of API is enhanced caused by vesicles targeted effect,

tardy clearance from the circulation & protection of API from natural surroundings.

- Non phospholipids vesicle having better stability than liposome.
- Easy hydrolysis of phospholipids due to ester bonds leads to migration of

phosphoryl group at stronger acidic area.

- Peroxidation of unsaturated phospholipids is also a type of degradation

Observed in liposome.

- Moreover, synthetic non-ionic surfactants are economical than phospholipids.

- Non ionic surfactant vesicles enhance stability of trapped API.
- Liposome and niosome having different properties since liposome is made up

by phospholipids while niosome is prepared from non ionic surfactant &

cholesterol [3].

Ideal properties of Non-ionic surfactant used in niosomes formation

Hydrophilic lipophilic balance & critical packing parameters of non ionic surfactant are important factors during vesicle formulation rather than micelles. The correlation among the surfactant structure containing size of polar headgroup plus length of non-polar region in vesicle preparation is illustrated in following figure. Hydrophilic lipophilic balance (HLB) is a good indicator of the vesicle forming ability of any surfactant, HLB number should not be more than 8, if it is increased hydrophilicity will increases so stability of vesicle decreases. If Non-ionic surfactants like polysorbates (tween) are used in formation niosomes have HLB more than 10, thus large concentration of cholesterol requires for stability of niosomes and which in turn results decrease in entrapment efficiency [4].

Classification of non-ionic surfactants

They are characterized as amphipathic (hydrophobic head and hydrophilic tail)

molecules capable for forming vesicle after hydrated in water or solution.

Sorbitan esters

They are prepared by sorbitol esters along with oleic acid anhydrides. Sorbitan esters are water insoluble as reflected by their lower HLB values [5].

Polysorbates

They are poly-oxy -ethylene derivatives of sorbitan ester. They are prepared by condensation of sorbitol ester with ethylene oxide moles. Polysorbates are water miscible due to high hydrophilic lipophilic balance value greater than 10.

Poly-oxy ethylated glycol mono-ethers

Poly-oxy ethylated glycol mono-ethers are available as Brij series which includes Poly-oxy ethyl lauryl ethers (Brij 30, 35) and Poly-oxy ethyl cetyl ethers (Brij 52, 56) General formula: Cx Ey

X: alkyl chain length and Y: ethylene oxide chain length

Poly-oxy ethylated alkyl phenols

Poly-oxy-ethylated t-alkyl phenols are available as Triton-X series which includes X- 114 (E 7-8), X-100 (E 9-10) and X-102 (E 12-13) [6].

Poloxamers

They are Poly-oxy-ethylene—Poly-oxy-propylene derivatives. They are commercially available under trade name 'Pluronics'. Pluronic F68 [Polyoxy propylene mol.wt.(1501-1800)+140 mol. ethylene Oxide]

Bola- surfactant

These novel surfactants are made up of azacrown ether units connected with long alkyl chain group and capable to form colloidal structure after addition of cholesterol [7].

According to the nature of lamellarity

* Multilamellar vesicles (MLV) 1-5 mm in size.

* Large unilamellar vesicles (LUV) 0.1 – 1μm in size

* Small unilamellar vesicles (SUV) 25 – 500 nm in size.

According to the size

* Small niosomes (100 nm – 200 nm)

* Large niosomes (800 nm – 900 nm)

* Big niosomes (2 μm – 4 μm)

Factors Affecting the Formation of Niosomes

Type of Surfactants

Initially, niosomes were formulated using cholesterol and single-chain surfactants such as alkyl oxyethylenes. The alkyl group chain length is usually from C12–C18. The hydrophilic- lipophilic balance (HLB) is a good indicator of the vesicle forming ability of any surfactant reported that the sorbitan monostearate (Span) surfactants with HLB values between 4 and 8 were found to be compatible with vesicle formation. The latest ones are similar to phospholipids and possess higher encapsulation efficiency. Esther type amphyphilic surfactants are also used for niosome formulation. They are degraded by esterases, triglycerides and fatty acids [8].

Cholesterol

Steroids are important components of cell membranes and their presence in membranes brings about significant changes with regard to bilayer stability, fluidity and permeability. Cholesterol, a natural steroid, is the most commonly used membrane additive and can be incorporated to bilayers at high molar ratios.

Other Additives

As is the case with liposomes, charged phospholipids such as dicethylphosphate (DCP) and stearyl amine (SA) have been used to produce charge in niosome formulations. The former molecule provides negative charge to vesicles whereas the later one is used in the preparation of positively charged (cationic) niosomes.

Nature of the Drug

The encapsulation of the amphipathic drug doxorubicin has been shown to alter the electrophoretic mobility of hexadecyl diglycerol ether (C16G2) niosomes in a pH dependent manner, indicating that the amphipathic drug is incorporated in the vesicle membrane [9].

Method of Preparation:

Niosomes can be prepared by various methods, including:

- Thin film hydration technique (Hand shaking method)
- Sonication
- Micro fluidization
- Reverse phase evaporation technique (REV**)**
- The "Bubble" Method
- Ether injection method

Thin film hydration technique (Hand shaking method): Non- ionic surfactant and cholesterol was taken in round bottom flask and dissolved in chloroform and ethanol. By shaking this mixture thin film is formed by rota at 50-100 rpm for 15-30 mins. Then later drug is dissolved in 10ml 7.4 buffer.Then vaccum is applied for 1hr at 600 pressure.Then results in formation of niosomes.

Ether injection method(EIM): Non- ionic surfactant was taken along with cholesterol and dissolved in diethyl ether which is mixed with methanol previously containing weighed quantity of drug.Then resulting solution was slowly injected using micro syringe at rate of 1ml/min into 10ml hydrating phosphate buffer.Then solution was stirred continuously with magnetic stirrer and temperature maintained at 60-65°c.The difference in temperature between the phases causes vapourization that results in formation of niosomes.

Sonication:A typical method of production of the vesicles is by Sonication of solution was introduced.

Micro Fluidization: Micro fluidization is a recent technique to prepare unilamellar vesicles of defined size distribution [10].

Evaluation Of Noisome

Optical microscopy: Observation of niosomes under projection microscope: Drop of niosomal suspension is taken on glass slide and observed under projection microscope magnification of 10x.

Mean vesicular diameter: The prepared eight formulations were characterized for mean vesicular diameter using Nano particle analyzer (Horiba Scientific Nano Partica SZ-100). A drop of niosomal sample was taken and mixed with double distilled water and sonication was kept for 1 hour. The analysis was performed at a temperature of 25°C [11].

Zeta potential: The prepared eight formulations were characterized for zeta-potential in order to know the stability of the formulations. The analysis was performed at a temperature of 25 °C with double distilled water as dispersion medium. From the results the formulations were found to be stable.

Determination of drug content: 1 ml of niosomal suspension was taken in a volumetric flask of 10ml and volume was made up by phosphate buffer pH7.4 and sonicated for 30 mins to obtain clear solution after that 1ml of this mixture was diluted to 10ml by phosphate buffer pH 7.4 and the percentage dug content was observed at 271nm using Uv spectrophotometer [12].

Determination of entrapment efficiency: In the ultracentrifugation method, the prepared niosomal suspension was subjected for centrifugation at high rpm. Analyze the clear supernatant liquid by using spectrophotometer and calculate the amount of unentrapped drug. Amount of entrapped drug can be obtained by subtracting amount of unentrapped from the total drug incorporated**.**

In vitro diffusion study: The in vitro drug diffusion studies can be carried out using Franz diffusion cells. A dialysis membrane was washed and soaked in phosphate buffer solution which act as a donar compartment and 50ml of 7.4 pH buffer was taken in the receptor compartment. The entire system was kept at 37±0.5˚c with continuous stirring at 100rpm. The samples were withdrawn at predetermined intervals and replaced by fresh medium simultaneously for time period of 12hrs. The amount of drug diffused from each formulation at specific time interval was determined using UV-spectrophotometer [14,13].

Niosome Delivery Applications

The most popular surfactants used are the sorbitan amphiphiles (Span 20, Span 40, Span 60 and Span 80) which incidentally are approved excipients [15].

Drug Targeting

Anti cancer drugs

Anti cancer drugs such as the model drug doxorubicin, when encapsulated in sorbitan monostearate poly (oxyethylene) coated (coated with Solulan C24) niosomes, circulate for prolonged periods The area under the plasma level time curve is increased six-fold by the niosomes when compared with the drug in solution, tumor levels are increased by 50% and tumoricidal activity is doubled. These particles circulate for prolonged periods due to the poly (oxyethylene) coating, which prevents particle recognition [54] and the uptake by the liver and spleen. Polyoxyethylene coat improve the tumoricidal activity of drugs such as doxorubicin, methotrexate and vincristine principally by altering drug biodistribution following intravenous administration such that the drug is targeted to some extent to the tumor tissue [16].

Anti infectives

The targeting of anti-leishmanial drugs to the liver, the site of pathology, is achievable with niosomal formulations. Hexadecyl triglycerol sodium stibogluconate niosomes are rapidly taken up by the liver producing peak levels of antimony that are twice that achieved with the drug in solution.The anti-parasitic activity of sodium stibogluconate is increased 10-fold by encapsulation into niosomes [17].

Delivery to the brain

Delivery of peptides to areas beyond the blood brain barrier is a major challenge, however, there is evidence that glucose coated niosomes may be able to achieve brain delivery of hydrophilic peptides [18].

Topical use of niosomes

Transdermal

The topical application of niosome encapsulated drugs results in the enhanced delivery of drugs through the stratum corneum and delivery is specifically enhanced when hydrophilic surfactants such as poly(oxye-thylene)-7-dodecyl ether or poly (oxyethylene)-8-lauryl ester are used to produce flexible or "elastic" vesicles, which have similar flexible bilayer properties to the phospholipid transfersomes [19].

Ocular

Niosomal formulations for the topical treatment of glaucoma have emerged in the form of Carbopol 934P coated sorbitan monostearate acetazolamide niosomes both chitosan and Carbopol 934P coated sorbitan monostearate timolol maleate niosomes and sorbitan monopalmitate timolol maleate discomes. Discome formulations with a particle size of 16/u.m produce a sustained lowering of intraocular pressure when compared with normal niosomes [20].

Localized Drug Action

Localized drug action results in enhancement of efficacy and potency of the drug and at the same time reduces its systemic toxic effects [21].

Conclusions

Niosomes are having great applications in the field of pharmacy. The stability of niosomes is considered to be more than liposome. Niosomal drug delivery will improve the solubility as well as permeability of the drug. Till date very few niosomal formulations are available in the market. Extensive research has to be done to establish its efficacy in cancer targeting

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