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NIOSOMES – NOVEL DRUG DELIVERY SYSTEM

[1]Akshay gole, [2]Dr. Ganesh Deshmukh, [3]Ajay Kulkarni, [4]Hrutuja padge

[1,3,4]Mpharm, Department of Pharmaceutics, oriental college of pharmacy, Sanpada, Navi-Mumbai, University of Mumbai.

[2]Associate professor, Department of Pharmaceutics, Oriental College of Pharmacy, Sanpada, Navi-Mumbai, University of Mumbai.

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Abstract:

Niosomes are basically a novel drug delivery system in which an encapsulated drug is given which improved its bioavailability by releasing the drug at particular site and increasing its therapeutic effect. The drug is release in controlled manner for long period of time and also at particular targeted site. various other drug delivery system such as liposomes, nanospheres, microspheres, etc. liposomes are first system but it shows number of drawbacks such as high cost and stability problems. Compare to liposomes, noisome are made of non-ionic surfactant vesicles system and it is better than liposomes. Other additives are cholesterol and charge inducing molecules. Niosomes are amphiphilic in nature they encapsulate both hydrophilic and lipophilic drug and it is affected by various factors during its formation. This review gives information about various methods of preparation, factors affecting, application to treat diseases and limitation.

Keywords: *Novel drug delivery system, Niosomes, Magic bullet, Non-ionic surfactant.*

Corresponding author:

Akshay Sunil Gole,

Department of Pharmaceutics,
Oriental College of Pharmacy, Sanpada,
Navi-Mumbai, University of Mumbai.

Email ID*: akshaygole7896@gmail.com*

Phone number*: 9594664780*

QR code

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INTRODUCTION:

The drug-delivery system is defined as a process of administering pharmaceutical compounds at a predetermined rate to achieve a therapeutic effect in humans or animals at diseased site, and at the same time, reducing the concentration of the medication in surrounding tissues.[1] The concept of "Magic bullet" which was proposed by Paul Ehrlich in 1909 refers to delivery of drug directly at targeted site of diseased cell without affecting the healthy cell. Development of new drug or improving its efficacy of existing drug is difficult, expensive and time consuming. No drug delivery system behaves to be ideally, but some attempts made to achive them by the novel drug delivery system. [2,3]

Novel drug delivery system aims to delivery drug at a rate directed by the needs of the body during the period of treatment and channel the active entity to the site of action. [4] Niosomes are novel drug delivery system, noisome are vesicles mainly consist of non-ionic surfactant, the reasons for preparing noisome is that it provides higher chemical stability than that of phospholipids, which are used in the preparation of liposome. [5]

Niosomes are synthetic microscopic vesicles consisting of aqueous core enclosed in a bilayer consisting of cholesterol and one or more non-ionic surfactant. Vesicles are prepared by hydration of non-ionic surfactants molecules. [6,7,8,9] The noisome are very small, microscopic in size and lie in nanometric scale. The particle size ranges from 10nm-100nm. They are structurally similar to liposomes in having a bilayer, however, the materials used to prepare noisome make them more stable and thus noisome offer many more advantages over liposomes. Niosomes can entrap both hydrophilic and lipophilic drugs and can prolong the circulation of the entrapped drug in body.

Structure of Niosomes-

Niosomes are basically microscopic lamellar structure consist of hydrophilic head and hydrophobic tail. The basic component used are non-ionic surfactant, cholesterol, and charge inducing molecules. [10,11]

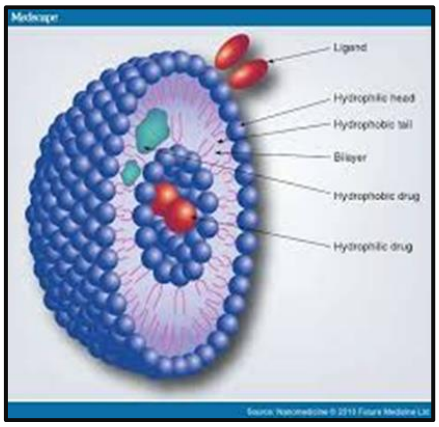

Figure 1: Structure of Niosome.

Surfactants-

Table 1: Surfactant used for making of non-ionic vesicles are as follows in given table: [12]

Non-ionic surfactant	Structural formulas
Cholestrolpoly (24) ox ethylene ether Dialkylpoly (7) glycerol ether	C16 H33¬ CH O (CH2CHO)7H | | CH2 CH2OH | C12H25O
Alkyl glucoside	H (CH2) n C6H11O6 n = 8,10,12,14,16,18
Hexadecylpoly (3) glycerol	C16 H 33 O (CH2CH2 O)3 H | CH2 OH
Cetyl mannoside	C16H33-- C6 H11O6
Cetyl lactoside	C16H33-- C6 H11O6
Alkyl galactoside	H (CH2) n- C6 H11 O6
Polyoxyetylenealkyl ether	H (CH2) n- (OC2H4) m OH n-12, 14,16,18 m-3, 4,5,6,7,8
n-Decylooxyethyleneoctadecylmyricylaminen-Decylooxyethyleneoctadecylmyricylamine	H (CH2)18-N- (C2H4O)10H | H (CH2) 13-C= O
Cetyldiglycerolester	C15H31CO-(OCHCH2)OCH2CHOHCH2OH | CH2OH

Characteristics of noisome-

- Biocompatible, Bio-degradable, non-immunogenic and non- carcinogenic.
- They are non- toxic, high resistance to hydrolytic degradation.
- The properties of noisome depend both on the composition of the bilayer and method of preparation.
- The ability of non- ionic surfactant to form bilayer vesicles is dependent on the HLB value of the surfactant.

Advantages of noisome [13,14,15,16]

- It offers greater patient compliance over oily based systems. Since the structure of the niosomes accommodate both hydrophilic, lipophilic as well as amphiphilic drug moieties, they can be used for a variety of drugs.
- A depot to release the drug slowly and offer a controlled release.
- They are Osmotically active and stable.
- It helps to increase the oral bioavailability of the drug.
- It also helps in increasing the skin penetration of the drug.
- They can be used for oral, parenteral as well topical.
- Handling and storage of noisome formulation doesn't require any special conditions.
- It helps in delivery of drug at particular site, hence targeted drug delivery system.

Disadvantages of noisome-

- Administration of sustained release medication does not have prompt termination of therapy.
- The physician has less flexibility in adjusting dosage regimen.
- Time consuming.
- It required specialised equipment for manufacturing.
- It leads to leaking of entrapped drug.

Method of Preparation:

The niosomes are prepared by the process of hydration of a surfactant and lipid mixture at elevated temperatures, followed by optional noisome size reduction in order to obtain a colloidal suspension. The method of preparation is chosen based upon the use of niosomes, since the preparation methods influence the numbers of bilayers, size, size distribution and entrapment

efficiency of the aqueous phase and the membrane permeability of the vesicles. There are several methods for preparation of niosomes which are as follows;

1. Ether injection method-

The method is based on slow injection of surfactant and cholesterol solution in ether through 14-gauge needle into a preheated aqueous phase maintained at 60°C. Vaporisation of ether resulting into formation of ether gradient at ether-water interface which leads to formation of single layered vesicles. Depending upon the conditions used the diameter of vesicles range from 50-1000nm.[11]

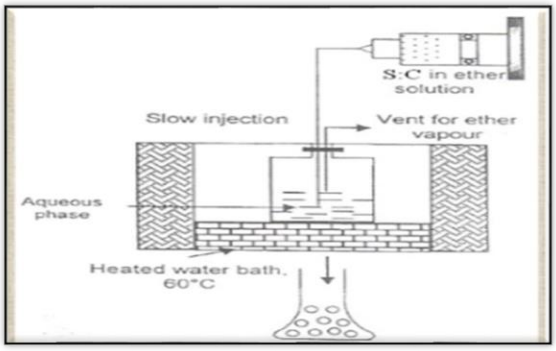

Figure 2: Ether injection method

2. Hand shaking method-[17,18]

Surfactant and cholesterol mixture are dissolved in 10ml diethyl ether in round bottom flask. The ether is evaporated under vacuum at room temperature in rotary evaporator upon hydration the surfactant swells and thin film of solid mixture deposited on the wall of flask. Surfactant film is then rehydrated with the aqueous phase at temperature slightly above the phase transition temperature of the surfactant use with gentle agitation. The process forms large multicellular vesicles.

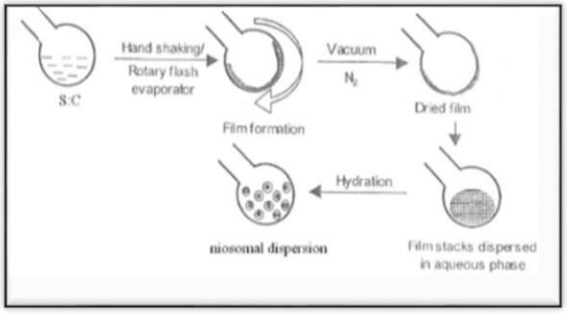

Figure 3: Hand Shaking Method.

3. Sonication Method-[19]

An aqueous phase is added to the surfactant/ cholesterol mixture in a glass vial. The mixture then probes sonicated for a certain time period. The resultant vesicles are small and uniform and unilamellar. In the case of niosomes the resulting vesicles size are in general larger than liposome, niosomes being no smaller than 100 nm in diameter.

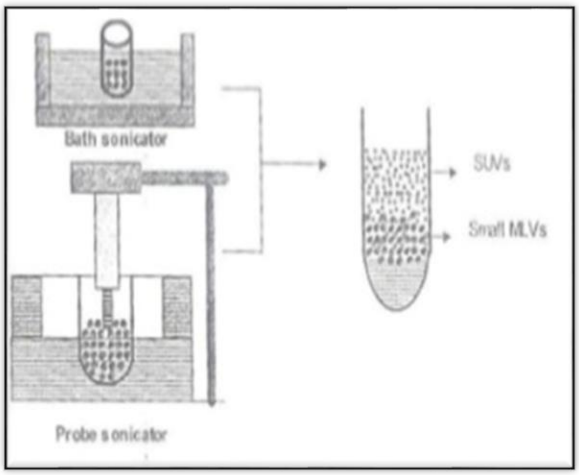

Figure 4: Sonication method.

4. Micro-fluidization method-[20]

This is new method for manufacturing of small MLV's. A micro fluidizer is used to pump the fluid at a very high pressure (10,000 psi). The two fluidised streams (one containing drug and other surfactant) are allowed to interact at high speed in micro channels in an interaction chamber. The high-speed impingement and the energy involved leads to formation of uniform and small niosomes. This method has a high degree of reproducibility.

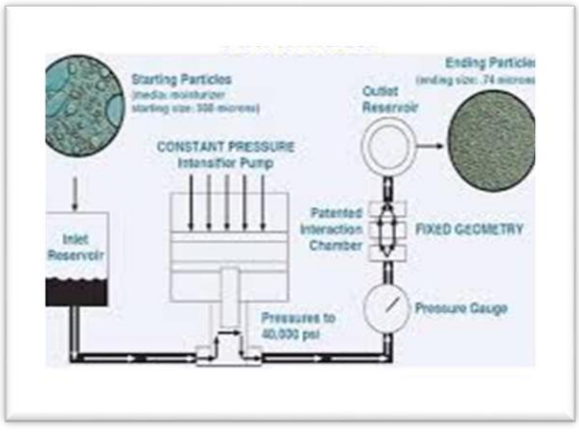

Figure 5: Micro-Fluidization Method.

5. Reverse phase evaporation method-

Cholesterol and surfactant are dissolved in ratio of 1:1 in mixture of ether and chloroform. An aqueous phase containing drug is added to this and the resulting two phases are sonicated at 4-

5°C. The clear gel formed is further sonicated after the addition of small amount of phosphate buffered saline (PBS). The organic phase is removed at 40°C under low pressure. The resulting viscous niosomes suspension is diluted with PBS and heated on the water bath at 60°C for 10 min to yield niosomes.[21]

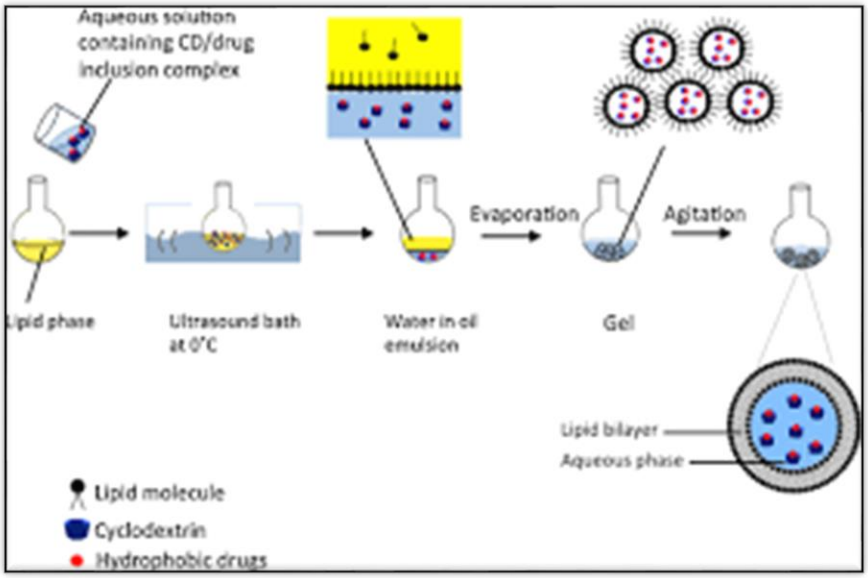

Figure 6: Reverse phase evaporation method

6. Bubble method-

It is novel technique for the one step preparation of liposomes and Niosomes without the use of organic solvents. The bubbling unit consists of round bottomed flask with three necks positioned in water bath to control the temperature. Water cooled reflux and thermometer is positioned in the first and second neck and nitrogen supply through third neck. Surfactant and cholesterol are dispersed together in this buffer(pH7.4) at 70oC, the dispersion mixed for 15 seconds with high shear homogenizer and immediately afterwards "bubbled" at 70oC using nitrogen gas.

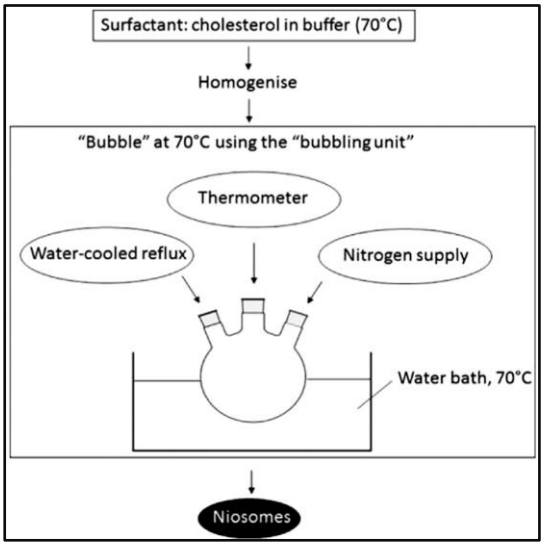

Figure 7: Bubble Method

Separation of unentrapped drug [22]-

The removal of unentrapped drug from the vesicle can be done by three method such as Gel filtration, Dialysis, Centrifugation.

Gel filtration-

The phosphate buffer solution or saline solution is used for the separation of unentrapped drug by using sepadex-G-50 column.

Dialysis-

The niosomal preparation is dialysed using phosphate buffer solution or saline solution to separate the unentrapped drug.

Centrifugation-

The niosomal suspension is centrifuged and supernatant is separated. The pellet is washed and the resuspended to obtain a niosomal suspension free from unentrapped drug.

Characterisation of niosomes-

Entrapment efficiency- [23,24]

After the preparation of noisome it is subjected to process of separation of unentrapped drug by gel filtration, centrifugation and dialysis. The remaining entrapped drug in niosomes is determined by lysing the vesicles using 50% n-propanol or 0.1% Triton X-100. The percentage of drug entrapped is calculated using the following formula:

$$\text{Percentage entrapment} = \frac{\text{Total drug} - \text{Diffused drug}}{\text{Total drug}} * 100$$

Measurement of angle of repose-
The funnel method is used for measurement of angle of repose of dry niosomes. The powder was poured into a funnel which was fixed at a position so that the 13mm outlet orifice of the funnel is 5cm above a level black surface. The powder flows down from the funnel to form a cone. By measuring the height of the cone and the diameter of its base the angle of repose is calculated.

Particle size-
Particle size of niosomes is very important characteristics. The surface morphology (roundness, smoothness, and formation of aggregates) and the size distribution of niosomes were studied by Scanning Electron Microscopy (SEM). Hu C. and Rhodes 7 in 1999 reported that the particle size of niosomes derived is approximately 6µm while that of conventional niosomes is about 14µm.[23,25]

Osmotic shock-
The change in the vesicle size can be determined by osmotic studies. Niosomes formulations are incubated with hypotonic, isotonic, hypertonic solutions for 3 hours. Then the changes in the size of vesicles in the formulations are viewed under optical microscopy.

Stability studies-
To determine the stability of niosomes, the airtight sealed vials are stored at different temperatures. were selected as parameters for evaluation of the stability, since instability of the formulation would reflect in drug leakage and a decrease. In the percentage drug retained. The niosomes were sample at regular intervals of time (0,1,2, and 3months) and observed for colour change, surface characteristics and tested for the percentage drug retained Surface characteristics and percentage drug retained after being hydrated to form niosomes and analysed by suitable analytical methods (UV spectroscopy, HPLC methods etc).

Physical stability of vesicles-
The vesicles preparation stored in glass vials at room temperature or in the refrigerator at 4°C for 3 months. The fusion of vesicles as the function of temperature is determined by change in vesicles diameter by laser light scattering method.

Therapeutic application-
There is very less marketed formulation found in the market. But some experimentally evaluated application of niosomal formulation has been identified in literature are as follows:

Anti-cancer drugs:
Methotrexate- The administration of drug by intravenous route l prepared from the C16G3 surfactants, did not lead to increased accumulation of the drug in the liver as compared to administration of free drug. This may be difference in size of the vesicles used in the two studies or to a modification of the drug in the liver compared to administration of free drug. The size, charge and hydrophilicity of the vesicles can change the distribution of the encapsulated drug when administered intravenously. The drug accumulation in the tumour cell was increased when administered in cholesterol containing vesicles.[26]

Doxorubicin- The Niosomes formulation prepared by the surfactant C16G3 with and without cholesterol were administered intravenously in S180 in tumour in mice. The size of vesicles is approximately 800-1000 nm in diameter. After a bolus injection in the tail vein of the rat, the concentration of doxorubicin in serum and the accumulation in lungs, liver, heart and spleen was determined. In serum a significant increase in doxorubicin concentration was observed then compared to the bolus injection of the free drug. [27]

Anti-leishmaniasis drug-
The leishmaniasis parasite mainly infects liver and spleen cells. The commonly used drugs antimonial may damage the body organ like heart, liver, kidney, etc. The efficiency of sodium stibogluconate has been found to be enhanced by incorporation in niosomes. [27]

Insulin-
The hypoglycaemic effect of insulin encapsulated in niosomes were determined in diabetic rats. Niosomes of different doses and different lipid compositions were prepared by lipid layer hydration method. The level of insulin was determined by HPLC method. In-vitro release and pharmacokinetics profile of niosomal formulation and free insulin were evaluated. The half-life was prolonged by 4-5 hours in contrast to free 2 hours for free drug. Noisome maintained the plasma insulin level up to 12 hrs but free drug was cleared quickly. More than 80 % of the drug was successfully encapsulated to give formulation with sustained release characteristics. [28]

Nasal drug delivery system:
The niosomes of Sumatriptan succinate was prepared using lipid hydration method. The noisome reported to enhanced the drug absorption & prolongation of action. [29]

Carrier of Haemoglobin-
Niosomes can be used as a carrier for haemoglobin. Vesicles were permeable to oxygen and could be modified to produce a haemoglobin dissociation curve similar to that of non-encapsulated haemoglobin. In addition, a niosomal suspension

showed a visible spectrum superimposable onto that of free haemoglobin.

Conclusion: Future prospects

From these reviews it is concluded that there are lots of scope to encapsulate toxic anticancer drugs, anti-infective drugs, anti-viral drugs, anti-inflammatory drug, etc. It is promising drug carrier to achieve better bioavailability and targeting the drug to particular site for action. It helps to reduce the toxicity and side effect of the drug. It does not any special storage condition hence it is stable, handling and transportation is easy.so far only in animal experiment of targeted drug delivery system is reported but further clinical trials in human volunteers can be carried to exploit the niosomes as prosperous drug carriers for targeting drug more efficiently for treating various diseases.

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