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# Niosome – A Novel Drug Delivery System

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**Abstract**

The concept of drug targeting or site specific drug delivery was introduced first time by Paul Elrich in 1909, when he reported 'magic bullet' to deliver a drug to the desired site of action without affecting the non target organs or tissues (Juliano, 1980) by associating the drug with a pharmacologically "inactive carrier" capable of conveying the drug selectively towards its target cells. The main goal of a site specific drug delivery system is not only to increase the selectivity and drug therapeutic index, but also to reduce the toxicity of the drug.

**Key-Word:-** magic bullet, inactive carrier, target cells, drug therapeutic index, site specific drug delivery system, toxicity.

## Introduction

Target oriented drug delivery systems are the areas of the major interest in the modern pharmaceutical research. The selective drug delivery to the target tissues increases the therapeutic efficacy of the drug and reduces its undesirable effect to non target tissues. The main goal of a site specific drug delivery system is not only to increase the selectivity and drug therapeutic index, but also to reduce the toxicity of the drug. (Widder *et al.*, 1982). Rheumatoid arthritis (RA) is a chronic, inflammatory condition of unknown eitiology that affects about 1% of general population (Feldmann *et. al.,* 1996) and is the most common cause of chronic inflammatory synovitis (Watson-Clark *et al.*, 1998). Although spontaneous remission can occur, it often progresses to chronic state associated with significant

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functional disability (Geletka and Clair, 2003). A number of drugs are used in the treatment of RA over the past 10-20 years. An ideal therapy in RA should ameliorate disease, prevent the development of extra-articular complications such as vasculitis, serositis and lung fibrosis and prevent premature death (Rabinovich, 2000).

**1.1)** *Merits Of Novel Drug Delivery System* **:**

1) Improved patient compliance resulting from the reduction in the frequency of doses required to maintain the desired therapeutic response.
2) Targeting of the drug molecule towards the tissue (or) organ reduces the toxicity to the normal tissues.
3) Pulsatile and pH dependent systems release the drug whenever the body demands.
4) Biocompatibility.
5) Economic and better savings are claimed from better disease management achieved with this system.

*1.2) Limitations of novel drug delivery system :*

Through there are number of advantages in NDDS system, there are a few factors that limit its usage.

1. Variable physiological factors such as gastrointestinal pH, enzyme activities, gastric and intestinal transit

   rates. The food and severity of patient's disease often influences drug bioavailability from conventional dosage forms and may interfere with the precision of control release and absorption of drug from such system.
2. The products which tend to remain intact may get lodged at some sites. If this occurs, slow release of the

   drug from the dosage form may produce a high localized concentration of drug causing local irritation.
3. The drugs having biological half-life of 1 hr. or less are difficult to be formulated as sustained release

   formulations. The high rate of elimination of such drugs from the body needs an extremely large maintenance dose which provides 8-12 hrs of continuous therapy.
4. These products normally contain a large amount of drug. There is a possibility of unsafe over dosage, if the product is improperly made and the total drug contained therein is released at one time or over too short time interval.

**Types Of Niosomes**

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The niosomes are classified as a function of the number of bilayer (e.g. MLV, SUV) or as a function of size. (e.g. LUV, SUV) or as a function of the method of preparation (e.g. REV, DRV). The various types of niosomes (Weiner *et al*., 1989) are described below.

i) Multi lamellar vesicles (MLV)

ii) Large unilamellar vesicles (LUV)

iii) Small unilamellar vesicles (SUV)

**(i)** Multilamellar vesicles (MLV): It consists of a number of bilayer surrounding the aqueous lipid compartment separately. The approximate size of these vesicles is 0.5-10 µm diameter. Multilamellar vesicles are the most widely used niosomes (Bangham *et al*., in 1974). It is simple to make and are mechanically stable upon storage for long periods. These vesicles are highly suited as drug carrier for lipophilic compounds.

**(ii)** Large unilamellar vesicles (LUV): Niosomes of this type have a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped with a very economical use of membrane lipids.

**(iii)** Small unilamellar vesicles: These small unilamellar vesicles are mostly prepared from multilamellar

vesicles by sonication method, French press extrusion method or, homogenization method. The approximate sizes of small unilamellar vesicles are 0.025-0.05 µcm diameter. They are thermodynamically unstable and are susceptible to aggregation and fusion. Their entrapped volume is small and percentage entrapment of aqueous solute is correspondingly low.

**Methods Of Preparation For Niosomes**

The methodology for niosome preparation has been evolved rapidly during the last few years as a response to prepare well defined niosomes for specific applications.

*3.1.1) Multi Lamellar Vesicles (Mlv)*

Bangosomes popularly known as multilamellar vesicles are prepared as per the method described by Bangham *et al*., 1974. In this method the lipids are dissolved in an organic solvent in a round bottom flask. A thin lipid layer is formed on the inside wall of the flask after removal of the organic solvent by rotatory evaporation at reduced pressure.

Multilamellar vesicles are formed spontaneously when an excess volume of aqueous buffer is added to the dry lipid. After shaking (by hand or vortex mixer), it results in formation of dispersion of multilamellar vesicles. Duration and intensity of shaking, the presence of charge inducing agents in the bilayer, ionic strength of the aqueous medium and lipid concentration are the important parameters influencing the size and the encapsulating efficiency of multilamellar vesicles. The lipids formed are quite heterogeneous both in size and in the number of lamella.

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*3.1.2) Small Unilamellar Vesicles (Suv)*

(A) Sonication: In this method, the preparation of small lamellar vesicles has been reviewed by Bangham (Bangham *et al*., 1974). The usual multilamellar vesicles and large unilamellar vesicles are sonicated either with a bath type sonicator or a probe sonicator, under an inert atmosphere (usually nitrogen or argon) to get the small unilamellar vesicles. During sonication, the multilamellar vesicles are broken down and small unilamellar vesicles with high radius of curvatures are formed.

(B) French press method: Dispersions of MLV's can be converted to small unilamellar vesicles by passage through a small orifice under high pressure (Berenholz *et al*., 1977). A French pressure cell was used by Hamilton and Guo in 1984. Multilamellar vesicles dispersion is placed in the French press and extruded at about 20000 psi at $4^{o}$C(Hamilton and Guo, 1984): On passing through the cell, a heterogeneous population of vesicles are formed ranging from several micrometers in diameter to small unilamellar vesicles size. Multiple extrusions results in a progressive decrease in the mean particle diameter (30-80nm) depending upon the pressure used. These niosomes are more stable than sonicated ones and can be used advantageously as drug delivery carriers.

(C) Ethanol injection method: An alternative method for producing small niosomes that avoids both sonication and high pressure is the ethanol injection method, first described by Batzri and Korn in 1973. In this method, the lipid is dissolved in ethanol and is rapidly injected into an excess of buffer solution or other aqueous medium though a needle. The force of the injection is usually sufficient to achieve complete mixing, so that the ethanol is diluted almost instantaneously in water and the phospholipids molecules are dispersed evenly throughout the medium.

*3.1.3) Large unilamellar vesicles (LUV)*

Large unilamellar vesicles provide a number of important advantages as compared to the multilamellar vesicles including high encapsulation of water soluble drugs with economy of lipid and reproducible drug release rates. However, large unilamellar vesicles are perhaps the most difficult type of niosomes to produce.

(A) Reverse phase evaporation method: Large Unilamellar vesicles can be prepared by forming water in oil emulsion of phospholipids and buffer in the excess organic phase followed by removal of the organic phase under reduced pressure. The two phases are usually emulsified by sonication. Removal of the organic solvent under vacuum causes phospholipid coated water droplets to cool and eventually form a viscous gel. The next step is to bring about the collapse of certain proportion of water droplets.

(B) Calcium induced method: This method is used to produce unilamellar vesicles and it is of high interest for the present investigation as it has the advantage of aggregation of small vesicles in the presence of calcium followed by subsequently fusion.

In this method (Papahadjopoulos *et al*., 1975) the drug encapsulation depends on the lipid concentration and approximately 30% of encapsulation of the drug is expected. The vesicles are obtained in the size range of 0.2-1 µcm diameter.

(C) Dehydration/rehydration of small unilamellar vesicles: In this method (Shew and Deamer,1985) sonicated vesicles are mixed in an aqueous solutions with the solute desired to be encapsulated and the mixture is dried under a stream of nitrogen. As the sample is dehydrated, the small vesicles fuse to form a multilamellar film that effectively sandwich's the solute molecules between successive layers. Upon rehydration, large vesicles are

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produced encapsulating a significant proportion of the solute. The optimal mass ratio of lipid to solute is approximately 1:2 to 1:3. This method has the potential application to large scale production, since it depends only on controlled drying and rehydration processes and does not require extensive use of organic solvents, detergents or dialysis system.

*3.2) Equipments Required For Preparation :*

*Given* in the table mention below (Table 1)

**Conclusion** *:*

Niosomes are efficient carriers for controlled drug delivery, to entrap hydrophilic drugs in the larger interior aqueous layer , whereas, lipophilic drugs in the outer lipid bilayer. Since, the niosomes, are biodegradable and non toxic and hence, a good carrier for targeting of therapeutic agents at the site of interest with reduced systemic toxicity.

The success of liposomal system has stimulated the search for other vesicle forming amphiphiles. Non-ionic surfactant vesicles (niosomes) are among the first alternative materials studied for the drug delivery.

Niosomes, the multilamellar vesicles made up of non-ionic surfactant with or without cholesterol surrounding aqueous compartments are one of those carriers.

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Table 1 : Equipments Required For Preparation

| **Sr. No.** | **Equipment** |
|---|---|
| 1. | UV-Visible Spectrophotometer |

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|---|---|
| 2. | Digital pH meter |
| 3. | Electronic Balance |
| 4. | Rotary vacuum evaporator |
| 5. | Microscope |
| 6. | Vacuum Pump |
| 7. | Magnetic Stirrer with hot plate |
| 8. | Research Centrifuge |
| 9. | Digital Vernier Caliper |
| 10. | Transmission electron microscope |
| 11. | Water Bath |
| 12. | Diffusion Cell |