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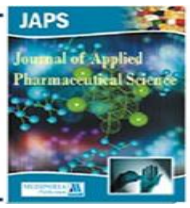

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Niosomal Drug Delivery System: The Magic Bullet

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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 methods of preparation of niosomes such as hand shaking, ether injection and sonication (developed on the basis of liposome production technique) have been reviewed by Khandare *et al.*, 1994. The hand shaking method form vesicles with greater diameter [0.35 – 13□m] as compared to those prepared by ether injection method [50-1000nm]. The film formation method was used for the preparation of the niosomes due to simplicity, reproducibility and high drug entrapment efficiency.

Keywords: Magic bullet, hand shaking, ether injection, sonication, film formation method.

INTRODUCTION

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) At present no available drug delivery system achieves the site specific delivery with controlled release kinetics of drug in predictable manner. Paul Ehrlich, in 1909, initiated the era of development for targeted delivery when he envisaged a drug delivery mechanism that would target directly to diseased cell. Since then, number of carriers were utilized to carry drug at the target organ/tissue, which include immunoglobulins, serum proteins, synthetic polymers, liposomes, microspheres, erythrocytes, niosomes etc. Among different carriers liposomes and niosomes are well documented drug delivery. Drug targeting can be defined as the ability to direct a therapeutic agent specifically to desired site of action with little or no interaction with nontarget tissue. Niosomes or non-ionic surfactant vesicles are microscopic lamellar structures formed on admixture of non-ionic surfactant of the alkyl or dialkyl polyglycerol ether class and cholesterol with subsequent hydration in aqueous media. In niosomes, the vesicles forming amphiphile is a non-ionic surfactant such as Span – 60 which is usually stabilized by addition of cholesterol and small amount of anionic surfactant such as dicetyl phosphate. Schematic representation of a drug targeting through its linkage to niosome via antibody is shown in figure 1.

Vanlerbeghe *et al.* (1972) first reported the niosomes as a feature of cosmetic industry. In 1979, Handjanivila *et al.* reported that the hydration of a mixture of cholesterol and single alkyl chain, resulted in formation of non ionic surfactant vesicular systems (i.e. Niosomes). Further, Okhata *et al.* reported the formation of such vesicles by dialkyl polyoxyethylene ether with non

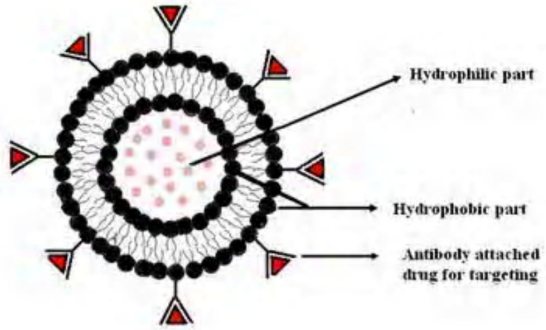


Figure 1: Niosome structure

ionic surfactants. Fendler (1982) published his work on ionic amphiphiles which were found to be toxic. Baillie and Azmin (Baille *et al.*, 1985, Azmin *et al*., 1985) brought the revolution by preparing vesicles with non ionic surfactants and studying various parameters. Since then, a number of non ionic surfactants were used to prepare vesicles viz. poly glycerol alkyl ether (Handjanivila *et al*., 1979 & Baillie *et al*., 1986), glucosyl dialkylether (Baillie *et al*., 1986), crown ethers (Kiwada. *et al*., 1985) polyoxytheylene alkyl ethers (Echegoyen *et al*., 1988 & Hofland *et al*., 1991), ester linked surfactants, Brij (Naresh *et al*., 1993 & Parthasarthi *et al*., 1994), and series of Spans and Tweens. (Naresh *et al*., 1993, Parthasarthi *et al*. 1994).

These non ionic surfactant vesicles can entrap both hydrophilic and lipophilic drugs, either in aqueous layer or in the vesicular membrane made of lipid materials, which can be used to prolong the circulation of the entrapped drugs. Due to the presence of non ionic surfactant and the lipid, there is a better targeting of drug(s) to tumor, liver and brain. Thus, they are useful in targeting of the drug for treating cancers, parasitic, viral and other microbial diseases more effectively.

These non-ionic surfactant based vesicles (niosomes) are regarded either as a inexpensive alternative of non-biological origin to liposomes or perhaps as a carrier system of drug physically similar to liposome *in vivo*, with specific properties to attain different drug distribution and release characteristics.

Rationale For Site Specific Drug Delivery (Tomilinson, 1991):

To reach previously inaccessible domains e.g. intracellular site, bacteria, viruses, parasites etc.

Exclusive drug delivery to the specific cells or diseased site in the body.

Reduction in the drug dose and side effects.

To control the rate and frequency of drug delivery at the pharmacological receptor.

To protect the drug and the body from one another until it reaches at the desired site of action.

Niosomally Entrapped Bioactive Agents

A variety of drugs/active agents have been encapsulated in Niosomes.

Table 1: various agents encapsulated in niosomes and the corresponding results.

Drug	Result	References
Estradiol	Enhanced *in vitro* skin permeation of pronisome formulations.	Fang *et al.*, 2001
Iopromide	Targeting of lopromide entrapped in MLV to the Kidney.	Erdogan *et al*., 1996
Flurbi profen	Enhanced bio-availability and anti-inflammatory activity of niosome encapsulated formulations as compared to conventional ointment base.	Reddy *et al.*, 1993
Timolol maleate	Sustained activity on ocular administration	Vyas *et al*., 1998
Cytarabine Hydrochloride	Niosomal encapsulation provides sustained release delivery.	Ruckmani *et al*., 2000
Rifampicin	Prolonged drug release	Kamath *et al*., 2000
Cisplatin	Significant antimetastatic activity	Gude, *et al*., 2002
Cytosine arabinoside	Effective release in acid environment	Roux *et al*., 2002
Tretinoin	Span 20 and Tween 80, Span 60 and Tween 80 combination gives good entrapment	Manconi *et al*., 2002, Desai and Finlay, 2002
Daunorubicin Hydrochloride	Improved therapeutic efficacy	Bala subramaniam *et al*., 2002
Colchicine	Sustain release & reduced toxic side effects	Hao *et al*., 2002.
Insulin	Sustained release after oral dosage form	Pardakhty *et al*., 2007
	Enhancing effect on vaginal delivery of insulin	Ning *et al*. 2005
	Improved stability against proteolytic enzyme	Varshosaz *et al*. 2003
Finasteride	Enhance drug concentration by topical application	Tabbakhian *et al*., 2006
Hydroxycamphothecin	Enhanced stability and antitumor activity.	Shi *et al*., 2006
Acetazolamide	Prolonged effect and decrease in Intraocular pressure	Guinedi et al., 2005
Clotrimazole	Sustain and controlled release of clotrimazale for local vaginal therapy	Ning et al., 2005
Timolol maleate	Improved pharmacodynamics	Agrawal and Kaur 2005
Tetanous Toxoide	Mannosylated niosomes were found to be useful oral vaccine delivery carrier.	Jain and Vyas, 2006
Propylthiouracil	Control the release of propyl thiouracil.	Suwakul et al., 2006.

Table 2: Various instrumentation requires for preparation of niosomes.

Sr. No.	Equipment	Manufacturer
1.	UV-Visible Spectrophotometer	Perkin Elmer EZ 301 Double beam
2.	Digital pH meter	Systronics
3.	Electronic Balance	A & D Japan
4.	Rotary vacuum evaporator	Steroglass, Italy
5.	Microscope	Olympus (India) Pvt. Ltd., Delhi
6.	Vacuum Pump	Ital Scientific, Genova
7.	Magnetic Stirrer with hot plate	Remi Sales & Engg. Ltd., Mumbai
8.	Research Centrifuge	Remi Sales & Engg. Ltd., Mumbai
9.	Digital Vernier Caliper	Mitutoyo digimatic, Japan
10.	Transmission electron microscope	Fei-Philips Morgagni 268 D
11.	Water Bath	Narang Scientific Works Pvt. Ltd., Delhi
12.	Diffusion Cell	Fabricated

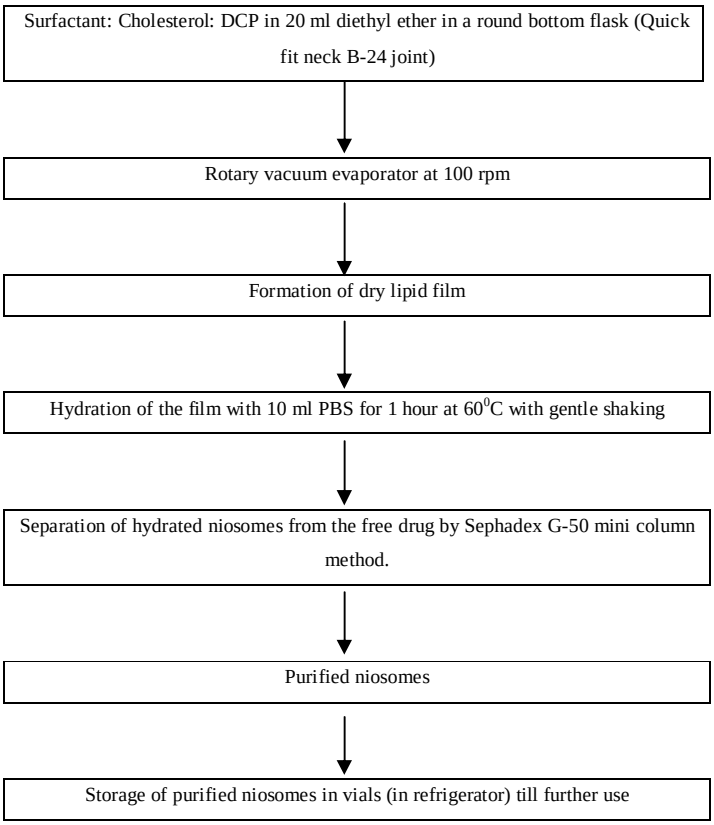
Instrumentation Require for Preparations

Various instrumentation requires for preparation of niosomes.

Method of Preparation

The entire process of preparation of niosomes has been shown in the flow diagram.

Flow Diagram 1: Flow diagram showing preparation of niosomes



APPLICATION

1) Targeting of bioactive agents

a) To reticulo-endothelial system (RES): The cells of RES preferentially take up the vesicles. The uptake of niosomes by the cells is also by circulating serum factors known as opsonins, which mark them for clearance. Such localized drug accumulation has, however, been exploited in treatment of animal tumors known to metastasize to the liver and spleen and in parasitic infestation of liver**.**

*b) To organs other than RES:*It has been suggested that carrier system can be directed to specific sites in the body by use of antibodies . Immunoglobulins seem to bind quite readily to the lipid surface, thus offering a convenient means for targeting of drug carrier . Many cells possess the intrinsic ability to recognize and bind particular carbohydrate determinants and this can be exploited to direct carriers system to particular cells.

2) Neoplasia Doxorubicin

The anthracyclic antibiotic with broad spectrum anti tumor activity, shows a dose dependant irreversible cardio toxic effect. Niosomal delivery of this drug to mice bearing S-180 tumor increased their life span and decreased the rate of proliferation of sarcoma . Niosomal entrapment increased the half-life of the drug, prolonged its circulation and altered itsmetabolism. Intravenous administration of methotrexate entrapped in niosomes to S-180 tumor bearing mice resulted in total regression of tumor and also higher plasma level and slower elimination .

3) Leishmaniasis

Niosomes can be used for targeting of drug in the treatment of diseases in which the infecting organism resides in the organ of reticulo-endothelial system. Leishmaniasis is such a disease in which parasite invades cells of liver and spleen. The commonly prescribed drugs are antimonials, which are related to arsenic, and at high concentration they damage the heart, liver and kidney. The study of antimony distribution in mice, performed by Hunter et al showed high liver level after intravenous administration of the carriers forms of the drug. Baillie et al reported increased sodium stibogluconate efficacy of niosomal formulation and that the effect of two doses given on successive days was additive.

4) Delivery of peptide drugs

Yoshida et al investigated oral delivery of 9-desglycinamide, 8-arginine vasopressin entrapped in niosomes in an in-vitro intestinal loop model and reported that stability of peptide increased significantly.

5) Immunological application of niosomes

Niosomes have been used for studying the nature of the immune response provoked by antigens. Brewer and Alexander have reported niosomes as potent adjuvant in terms of immunological selectivity, low toxicity and stability**.**

6) Niosomes as carriers for Hemoglobin

Niosomes can be used as a carrier for hemoglobin. Niosomal suspension shows a visible spectrum superimposable onto that of free hemoglobin. Vesicles are permeable to oxygen and hemoglobin dissociation curve can be modified similarly to non-encapsulated hemoglobin.

7) Transdermal delivery of drugs by niosomes

Slow penetration of drug through skin is the major drawback of transdermal route of delivery. An increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes. Jayraman et al has studied the topical delivery of erythromycin from various formulations including niosomes or hairless mouse. From the studies, and confocal microscopy, it was seen that non-ionic vesicles could be formulated to target pilosebaceous glands**.**

CONCLUSION

The concept of incorporating the drug into liposomes or niosomes for a better targeting of the drug at appropriate tissue destination is widely accepted by researchers and academicians. Niosomes represent a promising drug delivery module. They presents a structure similar to liposome and hence they can represent alternative vesicular systems with respect to liposomes, due to the niosome ability to encapsulate different type of drugs within their multienvironmental structure. Niosomes are thoughts to be better candidates drug delivery as compared to liposomes due to various factors like cost, stability etc. Various type of drug deliveries can be possible using niosomes like targeting, ophthalmic, topical, parentral, etc.

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