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FORMULATION AND CHARACTERIZATION OF NIOSOMES AS POTENTIAL NANOPARTICLES FOR DRUG DELIVERY

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Abstract

The therapeutic potential of many active substances is limited in clinical practice due to its disadvantageous physicochemical properties, pharmacokinetics and variable side effects causing low bioavailability and poor therapeutic concentration in the target tissue. An intriguing strategy to overcome these limitations is the design of nano-sized drug delivery systems. As a relatively new generation, vesicular systems especially niosomes are the most researched and characterized structures. Present study reports a detail review of data from clinical studies of different formulations of niosomes, methods of preparation and characterization of their structure, the influence of various parameters on the noisome stability and the market's patented formulations by now. We gathered the data needed for this study by searching relevant scientific and professional literature, made a comparison between niosomes and other vesicular nanosystems, listed the advantages and disadvantages and discussed the results of clinical studies on various active substances incorporated into niosomes.

Keywords: niosomes, drug delivery, nanoparticles, bioavailability

Introduction

Clinical implementation of highly lipophilic active substances is limited due to their instability in physiological pH, low aqueous solubility attributed with low systemic bioavailability. A promising strategy to overcome these limitations is incorporation in nano-sized delivery systems like niosomes.

The concept of niosomes was first introduced and patented by L'Oréal in 1970 in order to overcome the limitations of liposomes as vesicular systems. Vanlerberghe et al., who studied the interaction of nisomes with stratum corneum *in vitro* and *in vivo*, evaluated formulation and structure of niosomes in 1976. The obtained results showed higher skin elasticity in volunteers with dry skin compared with conventional emulsions (Vanlerberghe et al. 1972). In 1986 niosomal formulation was first used for drug delivery of antineoplastic agents (Cummigs et al. 1986, Hunter et al. 1986). Therefore, these facts led to higher interest for evaluation of the structure of niosomes not only for transdermal application but also for systemic application.

Niosomes as vesicular systems are composed of non-ionic surfactants and cholesterol suitable for incorporation of hydrophilic drugs into the aqueous compartment and lipophilic active substances into bilayer domains. Niosomes are formed by self-assembly of non-ionic surfactant and cholesterol in aqueous medium. Although liposomes are most studied nano-sized drug delivery devices, lack of stability and difficulties with sterilization led to development of niosomes as alternative controlled delivery system. The main differences between liposomes and niosomes are presented in Table 1 (Karim KM, et al. 2010, Marianecci et al., 2014).

Table 1. Comparison between liposomes and niosomes (ref)

Parameter	Liposomes	Niosomes
Stability	Non-stable attributed with lack of stability of phospholipids in liposomal membrane	Stable-attributed with higher stability of non-ionic surfactants
Price	Expensive	Economic
Toxicity	Reported cases of toxicity	Non-toxic
Size	10-3000 nm	10-1000nm
Storage	Special conditions	Without special storage conditions

As evident from the table, niosomes are promising candidates for topical, ophthalmic and systemic drug delivery.

Structure of niosomes

Generally, niosomes are composed of synthetic or semi-synthetic non-ionic surfactants with hydrophilic head and hydrophobic tail suitable for systemic application. The optimal candidates for niosome formulation are alkyl ethers or alkyl esters according to the low toxicity and commercial availability (Marianecci et al., 2014, Abdelkader et al., 2014). In order to increase the rigidity of the membrane and to improve the stability, cholesterol is also used as main component in niosomal membrane (Moghasemmi et al., 2014; Nasseri B., 2005,). The structure of niosomes is presented on Figure 1.

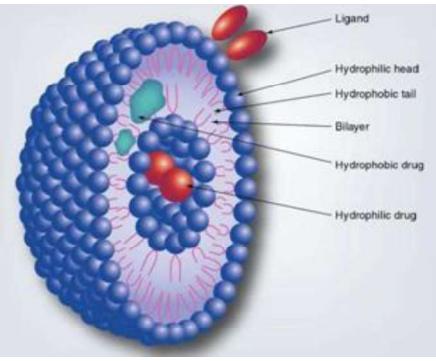

Figure 1. Structure of niosome

2.1 Alkyl esters: The most preferred non-ionic surfactants used for formulation of niosomal membrane are alkyl esters due to their low toxicity attributed with esterase degradation of the ester bond to fatty acid and triglycerides *in vivo* (Lawrence 2003). The promising candidates from this group are sorbitan esters (Span) and polyoxyethylene sorbitan fatty acid esters (Tween) widely used in pharmaceutical preparations (Varshosaz et al., 2003). Polyoxyethylene sorbitan fatty acid esters are more soluble compared with other vesicles, suitable for oral application (Hofland et al., 1992). Numerous studies confirmed the use of these surfactants. For example, polysorbate 60 is utilized for preparation of niosomes for oral delivery of diclofenac sodium, associated with prolonged release and protection of gastrointestinal mucosal membrane (Gawhari et al., 2015).

2.2 Polyoxyethylene alkyl ethers (Brij): Alkyl ethers are also utilized for formulation of niosomes. These non-ionic surfactants are characterized with relatively large polar head groups compared with their alkyl chain (Rajera et al., 2011). Because of their documented toxicity and local irritability, alkyl esters are more preferred nonionic surfactants for preparation of niosomal membrane (Pardakhty et al., 2007). In addition, limited use of alkyl ethers is associated with the reason that they cannot form vesicles without cholesterol because of the high solubility of polar groups (Abdelkader et al.,2010; Abdelkader, 2012). Despite the listed disadvantages, these surfactants are frequently used in many studies. In vitro study confirmed that niosomes prepared from alkyl ethers with film-hydration method are suitable for oral delivery of insulin without risk of degradation from pepsin, α-chymotrypsin and trypsin (Pardakhty A., et al 2007).

2.3 Cholesterol: Cholesterol is main component in niosomes used to stabilize its membrane. In combination with non-ionic surfactants, incorporation of cholesterol lead to higher rigidity and reduced permeability attributed with higher phase transition temperature. Prepared niosomes without cholesterol as a membrane component are exposed on risk of interaction with plasma proteins like albumin, transferrin and macroglobulin. Cholesterol is incorporated between the gaps of non-ionic surfactant, which consequently lead to increased rigidity of niosomal membrane. Mechanism of niosomal membrane stabilization composed of Tween 20 and cholesterol is illustrated on Figure 2 (Marianneci et al., 2014).

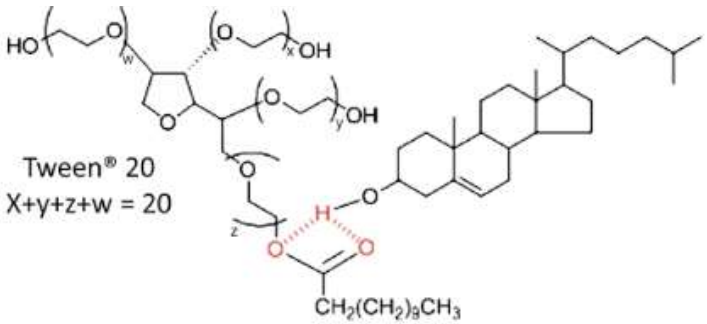

Figure 2. Interaction between Tween 20 and cholesterol (Marianneci et al., 2014)

The main mechanism of stabilization is possible hydrogen bonding interaction between 3-OH group of cholesterol and ester bond of the surfactant as presented on the Figure 2. In addition, incorporation of cholesterol is associated with higher zeta potential and electrostatic repulsion between the vesicles (Nematollahi et al., 2017). Maximum amount of added cholesterol varies widely, but numerous studies confirmed that optimal cholesterol concentration in niosomal membrane ranges from 30-50% in a ratio of 1: 1 to the non-ionic surfactant (Kazi K., et al. 2010).

Advantages and disadvantages of niosomes

Efficient drug delivery without toxicity to normal cells has always been a challenge in pharmaceutical technology. Therefore, nanoparticles as potential systems for delivery owe great potential for selective targeting and increased stability. During the last few decades, niosomes are used as a tool for improved drug delivery as a novel generation of vesicular systems. The advantages of niosomes are listed below (Buckton G., et al 1995; Mehanna et al., 2009, 2010;):

- Niosomes are osmotically active and stable nanoparticles suitable for incorporation of lipophilic and hydrophilic active substances
- Nanoparticles can be used as depot for sustained and controlled release of drugs
- Niosomes protect the active substances from proteolytic enzymes *in vitro*
- Niosomes are suitable for topical, ophthalmic and oral application
- Their membrane can be modified with ligands for targeted delivery
- Components of niosomal membrane are biocompatible, biodegradable and non-irritant
- Fabrication techniques are non-complex and economic

Despite the numerous advantages, niosomes possess several limitations that restrict their application for drug delivery. For example, niosomal shelf life can be abbreviated due to fusion and aggregation of niosomal dispersion that lead to leakage of the active substance. Furthermore, niosomes cannot be sterilized using heat sterilization and membrane filtration and aseptic preparation is required (Zuidamet al., 1993 Hathout et al., 2007;Abdelbary & El-gendy, 2008). Sometimes, preparation and characterization of niosomes is time consuming and need special equipment. Thus, in order to place commercially available niosomes on the market, further clinical investigation is required.

Conclusions

It is well-known fact that pharmacological effect of active substances is directly connected with its concentration in target tissue. Most active substances are characterized as highly lipophilic and instable in blood circulation, limitations that lead to necessity of higher dosage administration and accordingly undesired toxic effects. Encapsulation in niosomes solves the problems associated with low solubility and significantly improves the bioavailability and therapeutic concentration of the active substance. Therefore, niosomes as vesicular nanosystems can be used as promising platform for oral, ocular and transdermal delivery of drugs.

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