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An overview of characterizations and applications of proniosomal drug delivery system

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Abstract

Proniosomal drug delivery system is a stable vesicular system in nanotechnology to overcome the drawbacks associated with other vesicular systems. These are water-soluble pro-vesicular drug carriers coated with a non-ionic surfactant which on hydration give niosomes. The system is encapsulated and shows a systemic and targeted delivery of poorly soluble drugs with increased bioavailability and decreased side effects. Here we have covered characterizations and applications of the proniosomal drug delivery system.

Keywords: Provesicular; Proniosomes; Characterizations; Applications.

1. Introduction

Pro-vesicular drug delivery systems are the most efficient and approachable systems which have distinct advantages over conventional dosage forms. These carriers may serve as reservoirs of a drug that are capable to deliver a therapeutic amount of drug to the targeted site in the body. Poor solubility is a major physicochemical obstacle associated with many drugs and that can be overcome by developing a pro-vesicular drug delivery system. Novel drug delivery system plays an important role to control the release of drug at a predetermined rate or by maintaining a relatively constant drug at the site of administration and the presence of an effective concentration of drug also reduces the undesirable side effects [1-2]. Proniosomes overcome the problems of physical stability associated with other Vesicular and pro-vesicular drug delivery systems. The shelf life and stability of proniosomes are found to be better and prolonged in comparison to other vesicular systems.

2. Characterization of proniosomal vesicles

Proniosomal vesicles are tested for the following characterizations-

2.1. Vesicle morphology

The study of vesicle morphology is for the measurement of the size and shape of proniosomal vesicles. The size of proniosomal vesicles can be determined with and without agitation via the dynamic light scattering process. Without agitation, it forms the largest vesicle [3] (Fig. 1).

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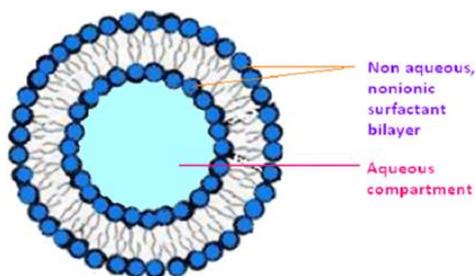


Figure 1 Structure of proniosomal vesicles [4].

2.2. Shape and surface morphology

Surface morphology is studied by scanning electron microscopy, optical microscopy, and transmission electron microscopy for its roundness, smoothness, and formation of aggregation.

2.3. Scanning electron microscopy

Scanning electron microscopy is used to demonstrate the role of cholesterol in the formation of the vesicle and is also used to study the shape and size of proniosomes. proniosomes suspension was sprinkled on double-sided adhesive carbon tape of an aluminum stub and also vesicles were spray-coated with gold/palladium and it is placed in the vacuum chamber of a scanning electron microscope. Then examine dry thin film of niosomal suspension using SEM equipped with a digital camera [5-6] (see Fig. 2a).

2.4. Optical microscopy

The proniosomal preparation was subjected to hydration with phosphate buffer of pH 7.4 and the niosomes formed from proniosomes were mounted on glass slides and the formed niosomes counted by optical microscope using hemocytometer viewed under a microscope with magnification for morphological observation after suitable dilution. The photomicrograph of the proniosomes is also obtained from the microscope by using a digital SLR camera [7] (see Fig. 2b).

2.5. Transmission electron microscopy

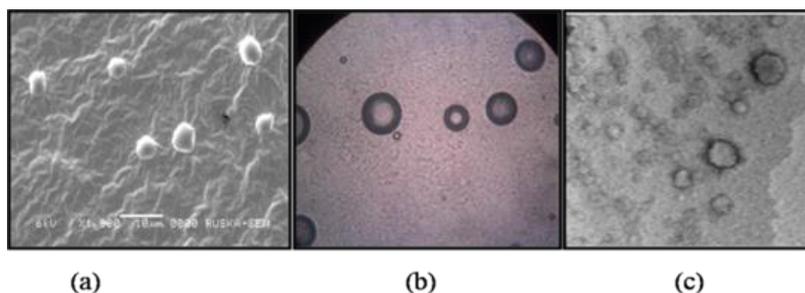


Figure 2 Images of proniosomal vesicles. By (a) Scanning electron microscopy[6], (b) Optical microscopy [7], (c) Transmission electron microscopy [8]

The surface morphology including smoothness, roundness, and formation of aggregation of hydrated niosome dispersion is determined using transmission electron microscopy. A drop of proniosomal dispersion is 10 times diluted using deionized water. A drop of diluted proniosomal dispersion is applied to a carbon-coated copper sheet of 300 mesh size and allowed for 1 minute so that some of the niosomes adhere to the carbon surface layer. The remaining dispersion is eliminated by adsorbing the drop with the corner of the filter paper. After rinsing 3-5 times the grid with deionized water twice and mixing a drop of 2 percent aqueous uranyl acetate solution for 1 second. The leftover solution is removed by absorbing the liquid with the tip of filter paper and the sample is air-dried [8]. The sample is observed by TEM at 80 Kv (see Fig. 2c).

2.6. Measurement of angle of repose

There are two methods or the measurement of the angle of repose for dried proniosomes

2.6.1. Cylinder method

In this method proniosomal powder formulation was poured into a cylinder which was fixed at a position 10cm above a leveled surface the powder is flowed down from a cylinder to form a cone on the surface and the angle of repose was then calculated by measuring the height of the cone and diameter of its base [9].

2.6.2. Funnel method

In this method, proniosomal powder preparation was poured into a funnel which was fixed at a position 10cm above the level surface and the powder is flowed down from the funnel to make a cone on the surface and the angle of repose was determined by measuring the height of the cone and diameter of its base [10] (see Fig. 3).

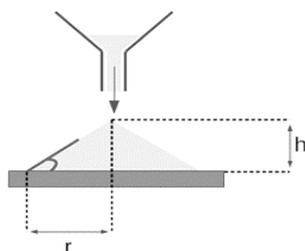


Figure 3 Representation of angle of repose.

The angle of repose is determined by using the equation-

$$\text{Angle of repose } (\theta) = \text{Tan}^{-1} (h/r)$$

Where 'h' is the height of the heap (mm) and 'r' is the radius of the heap (mm)

2.7. Rate of spontaneity (hydration)

The spontaneity of proniosomes formation is described by the number of niosomes formed after hydration for 15 mins of proniosomes. Transferred proniosomal formulation to the bottom of a small-stoppered glass tube and spread uniformly. Add 1 ml of pH 7.4 phosphate buffer along the walls of the test tube and kept aside without agitation. After 15 mins a drop of the hydrated sample was withdrawn and placed on Neubauer's chamber for counting range of niosomes eluted from a proniosomes [11].

2.8. Drug content

Proniosomal formulation equivalent to 250mg of drug was taken in a standard volumetric flask they were mixed with 50ml of solvent (methanol) by shaking and 1ml of the mixture was then diluted to 100ml with phosphate buffer pH 7.4. The absorbance was measured at a certain wavelength spectroscopically and drug content was calculated from the calibration curve [12-52].

2.9. Zeta potential analysis

Zeta potential of proniosomal formulation was determined by charge on vesicles & their mean zeta potential values with the standard deviation of 5 measurements. The diluted proniosomal dispersion was estimated by utilizing a zeta meter framework. By using a zeta potential analyzer based on the electrophoretic light scattering & laser Doppler velocimetry method. The high value of zeta potential will participate in better stability of the system [53-54].

2.10. The moisture content

The moisture content of proniosomes was determined by drying 3 gm of proniosomes in a Petri dish at 102°C for at least 5 hr. The samples were cooled in desiccators, weighed, and moisture content was determined on a dry weight basis [55].

2.11. Osmotic shock

This study is important to determine the changes in the size of the vesicle. In an osmotic shock study, the proniosomal formulations have to be incubated for 3 hr with different osmotic solutions like hypertonic, isotonic, hypotonic solutions. After 3hrs the changes in vesicle size were viewed under optical microscopy [56].

2.12. Penetration and permeation studies

Penetration and permeation of proniosomes can be visualized by confocal laser scanning microscopy (CLSM) [57].

2.13. Entrapment efficiency of proniosomes

The encapsulation efficiency of proniosomes is determined after the separation of an untrapped drug by dialysis, gel filtration, and centrifugation methods. The entrapment efficiency of proniosomal vesicular formulation is one of the important parameters to maintain the stability of drug. The vesicles obtained after removal of an untrapped drug by dialysis are then resuspended and it is determined by complete vesicle disruption using 50% n-propanol or 0.1% Triton X-100 and resultant solution analyze by appropriate assay method for the drug [57-60]. The percentage of drug entrapped in the vesicle is calculated by using the following formula.

$$\% \text{ Entrapment of drug in vesicle} = [\text{Total drug} - \text{diffused drug}] \div \text{Total} \times 100$$

2.14. Drug release kinetics and data analysis

In-vitro drug release study for proniosomal drug delivery is carried out by various kinetic equations to understand the kinetics and mechanism of drug release [61].

Zero-order, as cumulative % release vs. time,

$$C = K_0t$$

Where, K_0 = zero order constant expressed in units of concentration/time; t = time in hours.

Higuchi's model, as cumulative % drug release vs. square root of time.

$$Q = K_H t^{1/2}$$

Where Q = Cumulative amount of drug release at time ' t '; K_H = Higuchi drug release constant; t = Time in hours

In-vitro drug release study

2.14.1. Dialysis tubing

Dialysis tubing is a very important method to measure the *in-vitro* release of drug. The proniosomes are placed in prewashed dialysis tubing which can be completely sealed. The dialysis sac is then dialyzed against a suitable dissolution medium at room temperature which contained proniosomal preparation. At a suitable time interval, the samples are withdrawn and centrifuged to obtain the supernatant layer. The supernatant layer was taken and analyzed to determine the drug content using a suitable method. Maintenance of sink condition during this process is essential [62].

2.14.2. Reverse dialysis

In this technique number of small dialysis tubes are present containing 1 ml of dissolution medium are placed. The proniosomes are then uprooted into the dissolution medium. Direct dilution of the proniosomes is possible by this method and this method is rarely used for their slow release of drug [63-64].

2.14.3. Franz diffusion cell

This is another method for *In-vitro* drug release study by using Franz diffusion cell. In this method, proniosomal formulations are placed in the donor chamber of a Franz diffusion cell fitted with a cellophane membrane. The maintenance of sink condition is very useful. The proniosomes are then dialyzed against proper dissolution medium at a definite temperature; the samples are then withdrawn from the medium at suitable intervals and analyzed for drug content using appropriate techniques like UV spectroscopy, HPLC, etc. [65].

2.15. *In-vivo* drug release study

In vivo studies of proniosomal formulation can be carried out by using different grades of animals like rats, mice, rabbits, and guinea pig. Drug release from proniosomes derived vesicles can follow only desorption from the surface of vesicles or diffusion of the drug from bilayer membrane and may also follow a combined desorption and diffusion mechanisms [66].

2.16. Stability studies

Stability studies of proniosomes are carried out by storing the formulated proniosomal formulations at various ambient temperatures such as at refrigeration temperature (2-8°C), at room temperature (25±0.5°C), and elevated temperature (45±0.5°C) from a period of 1-3 months. All important evaluation parameters related to proniosomes are periodically monitored. According to ICH guidelines stability studies for dry proniosomes powder meant for reconstitution should be studied for accelerated stability at 75% relative humidity as per ICZ and climatic conditions. For long term stability studies the temperature is 25 °C/60% RH for the countries in a zone I and II and for the countries in zone III and IV the temperature is 30°C/65% RH. The product should be evaluated for its appearance, color, assay, pH, preservative content, particulate matter, sterility, and pyrogenicity [67-68].

3. Applications of proniosomes

3.1. Antibacterial therapy

Proniosomal preparations are used for antibacterial therapy, during the storage of an anti-bacterial drug which increases the physical stability and prevents the oxidation of formulation [2].

3.2. Studying immune response

Proniosomes are used in the study of immune response due to their immunological selectivity, better stability, and lower toxicity. The nature of immune response provoked by antigens studied by proniosomes [2].

3.3. Anti-neoplastic treatment

Most of the antineoplastic drugs may cause severe side effects. Proniosomes carrier can alter the metabolism as well as prolong the circulation and half-life of the drug, thus decreasing the side effects of the drugs. Also, proniosomes are widely used in cancer therapies [69].

3.4. Cosmetics or cosmeceuticals

In Cosmetics proniosomes are used as an effective delivery due to their unique properties like they non-toxic, dermatologically acceptable, control the release of a drug, also enhances the penetration of the drug via the skin layer. Proniosomal gel formulation mainly shows advantages in cosmetics. The therapeutic agents which can be incorporated in proniosomal carrier systems are- cleansing, moisturizing, sunscreen particles, nutritional, anti-wrinkle, anti-aging agents, etc. [70].

3.5. Proniosomes as carriers for hemoglobin

Proniosomes are used as carriers for hemoglobin within the blood. The proniosomes are permeable to oxygen and hence can act as a carrier for hemoglobin in disease conditions [71].

3.6. In NSAID application

The Non-steroidal anti-inflammatory drug like Ketorolac tromethamine can be given in the form of proniosomal preparation by transdermal route to maintain the drug blood levels for an extended period for postoperative pain (65).

3.7. Localized drug action

Drug delivery through proniosomes is used to achieve localized drug action, results in enhancement of efficacy and potency of the drug. At the same time reduces its systemic toxic effect [71].

3.8. Cardiological application

Proniosomes are used as carriers for cardiac active drugs. Mainly captopril drug is given by transdermal route for the treatment of hypertension and is also helpful to extended-release of the drug in body [72].

3.9. Drug targeting

One of the most helpful aspects of proniosomes is their ability to target or focusing drugs e.g. most of the vesicular formulations are utilized to treat tumors in animals known to metastasize the liver and spleen [73].

3.10. Treatment of leishmaniosis

Leishmaniosis can be treated with antimony derivative by delivering the drugs through proniosomes [74].

3.11. Delivery of peptide drugs

It is investigated that proniosomal formulations are useful in the delivery of peptides that protect it from gastrointestinal peptide breakdown [75].

3.12. Transdermal drug delivery systems

Proniosomal formulation is mostly suitable for transdermal drug delivery that greatly enhances the uptake of drugs through the skin. This technology is widely used in cosmetics. Recently transdermal vaccines by proniosomal technology are also being researched [76].

3.13. Hormonal therapy

It was found that the work had been performed on proniosomes based transdermal delivery of levonorgestrel is the emergency contraceptive [77].

3.14. Sustained release

The sustained release effect of proniosomes can be applied to drugs with low therapeutic index and low water solubility since those could be maintained in the circulation via proniosomal encapsulation [78].

3.15. Patents filed

There are several Patents related to proniosomes and niosomes. Some are mentioned in Table 1.

Table 1 Patents related to proniosomes and niosomes.

Patent No.	Inventors	Title	Ref
US 4830857A	R. Handjani, A. Ribier, G. Vanlerberghe, A. Zabotto, J. Griat	Cosmetic and pharmaceutical compositions containing niosomes and a water-soluble polyamide, and a process for preparing these compositions	[79]
US 6051250	Ribier, A. Simonnet, Jean-thierry	Process for the stabilization of vesicles of amphiphilic lipid (s) and composition for topical application containing the said stabilized vesicle	[80]
US 06576625B2	A. Singh, R. Jain	Targeted vesicular constructs for cytoprotection and treatment of H. pylori infections	[81]
US 06951655B2	Y. Cho, K. H. Lee	Pro-micelle pharmaceutical compositions	[82]
WO/2010/12346	Madhavan, Eva-Kathrin	Madanagopal. Vesicular Systems and Uses	[83]
US 5720948	Goyal C, Ahuja M	Non-ionic surfactant emulsion vehicles and their use for deposition of drug into and across skin	[84]
US 20070172520	Michael VanAuker, Anna Plaas, Elizabeth Hood	Immuno-targeting of non-ionic surfactant vesicles	[85]

4. Conclusion

This carrier mechanism has enormous opportunities in dermatology for the treatment of skin disorders such as melanoma, psoriasis, bacterial and fungal infections. These do not require any special handling and storage environment. Further exploration and research need to be developed on the niosomal and proniosomal preparations, which help to be accessible the products commercially.

Compliance with ethical standards

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Disclosure of conflict of interest

None.

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