Available online at www.elixirpublishers.com (Elixir International Journal)

Pharmacy

Elixir Pharmacy 78 (2015) 29720-29724

ISSN: 2229-712X

Proniosomes: a preferable carrier for drug delivery system

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ARTICLE INFO

Article history:

Received: 15 August 2011;

Received in revised form:

21 December 2014;

Accepted: 9 January 2015;

Keywords

Proniosome,

Noisome,

Lipid vesicles,

Non-ionic surfactant.

ABSTRACT

In recent time, proniosomal and noisomal system have been received a great attention in drug delivery applications as well as in pharmaceutical research. In order to minimize the problems associated with niosome physical stability such as aggregation, fusion and leaking and to provide additional convenience in transportation, distribution, storage and dosing etc, a dry product can be prepared, which is called proniosome. Proniosomes are dry formulation using suitable carrier coated with nonionic surfactants and can be converted into niosomes immediately before use by hydration. These proniosome-derived niosomes are as good as or even better than conventional niosomes. The current review deals with the trends, different aspects and the future perspective in the development of proniosomal drug delivery systems.

Introduction

Proniosomes are solid colloidal carrier particles that are coated with surfactants and can be measured out as needed and dehydrated to form niosomal dispersion immediately before use on brief agitation in hot aqueous media within minutes [1-2]. Proniosomes are more advantageous than nonionic surfactant vesicles i.e., noisomes, in terms of physical stability such as aggregation, fusion and leaking, and provide additional convenience in transportation, distribution, storage, and dosing [3]. These carriers can act as drug reservoirs and the rate of drug release can be controlled by modification of their composition. These carriers enable to entrap both hydrophilic and lipophilic drugs and also known as drug reservoir. Ease of transfer, distribution, measuring, and storage make proniosomes a versatile delivery system with potential for use in drug delivery applications due of their capability to carry a variety of drugs [4], drug targeting [5], controlled release [6] and permeation enhancement of drugs [7]. The current review deals with the trends, different aspects and the future perspective in the development of proniosomal drug delivery systems.

Niosomes

Niosomes are non-ionic surfactant vesicles that are capable to entrap hydrophilic as well as lipophilic drug candidates because they have an infrastructure consisting of both hydrophilic and hydrophobic moieties together. Niosomes are also osmotically active, stable, providing the stability of entrapped drug [8-10]. They are advantageous than other vesicles as being cheap and chemical stability. All methods traditionally used for preparation of niosomes are time consuming and many of them need specialized equipments. Most of these methods allow only for a predetermined lot size, so material is often wasted if smaller quantities are required for particular dose application [11]. The size of niosomes is microscopic and lies in nanometric scale. The particle size ranges from 10-100 nm. Transdermal therapeutic systems have generated an interest as these systems provide the considerable advantage of non-invasive parental routes for drug therapy, avoidance of first-pass gut and hepatic metabolisms, decreased side effects and relative ease of drug input termination in problematic cases [12]. Niosomes also suffer from some limitations:

1.Physical instability;

2.Aggregation;

3.Fusion;

4.Leaking of entrapped drug; and

5.Hydrolysis of encapsulated drugs which limits the shelf life of the dispersion

Hence to overcome the drawback, the researchers are focus on the development of proniosomes and converted them into niosomes.

Proniosome-derived niosomes

Hu and Rhodes et al. reported that proniosomes are dry formulations of surfactant-coated carriers, which can be rehydrated by brief agitation in hot water [13]. These carriers have capacity to minimize the problems associated with noisome. Proniosome-derived niosomes are much better than conventional niosomes, which provide optimal flexibility, unit dosing, easy processing and packaging. In the stability point of view, dry proniosomes is supposed to be more stable than a pre-manufactured niosomal formulation. Size distributions of proniosome-derived niosomes are also superior to conventional noisome and as well as release performance [14-15]. Proniosomes are found as dry powder and thus, could be dispensed in capsule form.

Material for the preparation of proniosomes

Proniosomes are product of nonionic surfactants and easily prepared by dissolving the surfactants in a minimal amount of an acceptable solvent and least amount of water. Typically, proniosomes may contain various nonionic surfactants like spans, tweens, lecithin, alcohols (ethanol, methanol, isopropyl alcohol etc) and chloroform.

Drug entrapment efficiency (DEE) in proniosomes is influenced by chemical structures of nonionic surfactants and DEE is expected to be increased with increment of alkyl chain of nonionic surfactants [16]. It has also been reported that spans have capacity to contribute highest phase transition temperature,

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which may provide highest entrapment for the drug molecules and vice-versa [17]. It has been found that the drug entrapment capacity of spans containing vesicles is higher in comparison to tweens containing vesicles [18]. Most of the surfactants used to make nonionic surfactant-based vesicles have low aqueous solubility. However, freely soluble nonionic surfactants such as tweens can form micelles on hydration in presence of cholesterol [19]. Again, cholesterol imparts stability and permeability of vesicles [20-21]. In addition, nonionic surfactant and cholesterol can be combined with lecithin in these preparations; whereas formulations containing lecithin increase the DEE compared to formulations containing cholesterol, only [22]. However, the incorporation of lecithin into the formulation requires some special treatment during preparation and storage, which makes the product less stable and highly expensive [20]. As stated earlier, proniosomes require minimal amount of acceptable solvents like ethanol, methanol, isopropyl alcohol, chloroform, etc for dissolving surfactants. Various examples of different component of proniosomes are enlisted in Table 1 along with their use.

Method for preparation of proniosomes

Proiosomes can be prepared by two ways, such as:

Spraying method

Proniosomes can be prepared by spraying surfactants in organic solvents containing sorbitol powder, and then evaporating the solvent. Because the sorbitol carrier is soluble in the organic solvent and this process is continued until the desired surfactant load has been achieved. The surfactant coating on the carrier comes out to be very thin and hydration of this coating allows multilamellar vesicles to form [13].

Advantages:

Simple method and suitable for hydrophobic drug without concerns of instability or susceptibility of active pharmaceutical ingredient to hydrolysis.

Disadvantages:

a)If the coating of surfactant solution was applied too quickly, the sorbitol particles would degrade and sample becomes viscous slurry.

b)This method was reported to be tedious since the sorbitol carrier for formulating proniosomes is soluble in the solvent used to deposit the surfactant

Slurry method

Slurry method is used to prepare proniosome using maltodextrin as a carrier. In slurry method, the entire volume of surfactant solution is added to maltodextrin powder in a rotary evaporator and vacuum applied until the powder appears to be dry and free flowing. The niosomes can be derived from drug containing proniosome by adding drug to the surfactant mixture prior to spraying the solution onto the carriers (like sorbitol, maltodextrin, etc) or by addition of drug to the aqueous solution used to hydrate the proniosomes [15].

Advantages:

a)Due to uniform coating on carrier it protects the active ingredients and surfactants from hydrolysis and oxidation etc.

b)The higher surface area results in a thinner surfactant coating, which makes the rehydration process more efficient.

Disadvantages:

a)Method is time consuming and involves specialized equipment with vacuum and nitrogen gas.

b)The thin film approach allows only for a predetermined lot sizes so material often wasted so small quantities or small dose batch can be tedious one.

Formation of niosomes from proniosomes

The niosomes are generally prepared from the proniosomes by adding the aqueous phase to the proniosomes with brief agitation at a temperature greater than the mean transition phase temperature of the surfactant.

Method for the separation of unentrapped drug

During preparation of noisome some amount of drug are being unentrapped, so determination of unentrapped drug are very essential .The removal of unentrapped solute from the vesicles can be accomplished by various techniques, which include:

i.Dialysis: At first the aqueous niosomal dispersion is dialyzed in dialysis tubing against suitable dissolution medium at room temperature after that the samples are withdrawn from the medium at suitable time intervals, centrifuged and analysed for drug content using suitable methods like UV spectroscopy, HPLC, etc [28-29].

ii.Gel Filtration: Gel filtration techniques is used to separate unentrapped drug through a Sephadex-G50 and eluted with suitable mobile phase and analyzed with suitable analytical techniques [17, 30].

iii.Centrifugation: The unentrapped drug of the proniosome derived niosomal suspension is separated by centrifugation as supernated is separated. The pellet is washed and then resuspended to obtain a niosomal suspension free from unentrapped drug [29].

Evaluation of the parameters of proniosomes

i. DEE

DEE of the proniosomal dispersion can be estimated by separating the unentrapped drug by dialysis [28-29], centrifugation [29], or gel filtration [17, 30] as described above and the drug remained entrapped in niosomes is determined by complete vesicle disruption using 50 % n-propanol or 0.1 % Triton X-100 and analyzing the resultant solution by appropriate assay method for the drug [13, 31]. The DEE can be calculated as follows:

DEE (%) = [Entrapped drug / Total drug] × 100

ii. Angle of repose

The angle of repose of dry proniosome powder is measured by a funnel method.

In this method, the funnel is fixed at a position so that the 13 mm outlet orifice of the funnel is 10 cm above a level black surface.

The powder is poured through the funnel to form a cone on the surface, and the angle of repose is then calculated by measuring the height of the cone and the diameter of its base.

iii. Vesicle size and vesicle size distribution

Drug permeability is dependent on vesicle size. Therefore, vesicle size vesicle size and vesicle size distribution of proniosomes are necessary. To determine average vesicle size and vesicle size distribution, instruments used mainly are:

a)Malvern Mastersizer [32];

b)Optical microscopy[33];

c)Laser diffraction particle size analyzer [1];

d)Coulter submicron size analyzer [18].

iv. Vesicle shape and surface characterization

To determine vesicle shape and for surface characterization, instruments used are:

a)Optical microscopy [33];

b)Transmission electron microscopy (TEM) [32];

c)Scanning electron microscopy (SEM) [34].

v. Rate of hydration

To determine the rate of hydration Neubaur's chamber is used [35].

vi. Zeta potential

To analyze the colloidal properties of proniosomal formulations, zeta potential value determination is necessary. Zeta potential can be determined by Malvern Zetasizer [32].

vii. In-vitro Drug release from proniosomes

In vitro drug release from the proniosome can be evaluated by:

a)Dialysis tubing

b)Reverse dialysis

c)Using Franz diffusion cell

Dialysis Tubing: Muller et al., (2002) reported that the in vitro drug release could be achieved by using dialysis tubing. The proniosomes is first placed in prewashed dialysis tubing which can be hermetically sealed.

Then proniosome suspension is dialyzed through dialysis sac against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, centrifuged and analyzed for drug content using suitable analytical method. The study requires sink condition to be maintained [36].

Reverse Dialysis: In this technique a number of small dialysis bags containing 1 ml of dissolution medium are kept in proniosomes. The proniosomes are then displaced into the dissolution medium. The drug release can be quantified with direct dilution of proniosome [36].

In vitro release study using Franz diffusion cell: The in vitro diffusion studies are generally performed by using Franz diffusion cell. Proniosomes are placed in the donor chamber of a Franz diffusion cell fitted with dialysis membrane or biological membranes.

The entrapped drugs get permeated through the dialysis membrane from donor chamber to receptor chamber containing a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals, and analyzed for drug content using suitable analytical methods [4].

In vitro drug release kinetics and mechanism: In order to understand the kinetic and mechanism of drug release, the result of in-vitro drug release study were fitted with various kinetic equations like: zero order, first order, Higuchi's model and Koresmeyer-Peppas Model.

Zero-order Kinetics: $F = Ko\ t$; where, F represents the fraction of drug released in time t, and Ko is the zero-order release constant.

First-order Kinetics: $\ln (1-F) = - K1\ t$; where, F represents the fraction of drug released in time t, and K1 is the first-order release constant.

Higuch Model: $F = KH\ t1/2$; where, F represents the fraction of drug released in time t, and KH is the Higuchi dissolution constant.

Koresmeyer-Peppas Model: $F = Kp\ tn$; where, F represents the fraction of drug released in time t, and Kp is the Koresmeyer-Peppas release rate constant and n is the diffusion exponent.

The Korsmeyer-Peppas model was employed to determine the mechanism of drug release from the formulation. Type of diffusion can be categorized on the basis of diffusion exponent like: Fickian (non-steady) diffusional when $n \leq 0.5$ and a case-II transport (zero-order) when $n \geq 1$. And the in between 0.5 and 1 are indicative of non-Fickian, 'anomalous' release [37-38].

viii. Osmotic shock

This study is important to assess the change in vesicle size viewed under optical microscope after incubation with hypnotic, isotonic, hypotonic solutions for 3 hrs [10].

ix. Stability studies

Stability studies of proniosomal formulations were carried out by keeping at various temperature conditions like refrigeration temperature (2-8°C), room temperature (25 ± 0.5°C) and elevated temperature (45 ± 0.5°C) from a period of one month to three months. Drug content and variation in the average vesicle diameter were periodically monitored [5, 33, 35].

ICH guidelines suggests stability studies for the dry proniosome powders meant for reconstitution that should be studied for accelerated stability at 40°C/75 % RH (relative humidity) as per international climatic zones and climatic conditions (WHO, 1996). According to ICH guidelines, for long term stability studies the temperature is 25°C/60 % RH for the countries in zone I and II and for the countries in Zone III and IV the temperature is 30°C/65 % RH. Product should be evaluated for appearance, colour, assay, pH, preservative content, particulate matter, sterility and pyrogenicity.

Application of Proniosome

Drug targeting

Proniosomes has the ability to target the drugs and can be used to target drugs to the reticulo-endothelial system (RES) because the RES preferentially takes up proniosome vesicles [40]. The uptake of proniosomes is controlled by circulating serum factors called opsonins. These opsonins are useful marker substances for niosose clearance. Proniosomes target and localize the drug in higher concentration to treat tumors cells in animals especially in liver and spleen tumors and also can be used for parasitic infection of liver [11]. It has been found that if a carrier system (such as antibodies) can be attached to proniosomes (as immunoglobulin bind readily to the lipid surface of the proniosome) to target them to specific organs [40].

Antineoplastic treatment

Antineoplastic drugs are generally known as cytotoxic drugs and it produces severe side effects. proniosome can reduce the side of these drugs by altering the metabolism through prolong circulation and half life of the drugs. Two separate studies showed that noisome containing doxorubicin and methotrexate [41-42] gave beneficial effect over the unentrapped drug and also showed reduction in proliferation rate of tumor cells and achieving higher plasma level with slower elimination [43].

Antiparasitic Treatment

A leishmania parasite commonly infects liver and spleen and derivatives of antimony (antimonials) are primarily used for the treatment but higher concentrations of these are always harmful for our sensitive organs like heart, liver, kidney etc. Hunter et al., (1988) reported that the proniosome containing sodium stibogluconate showed greater efficacy in treatment as well as lower the side effects [44].

Delivery of peptides

Delivery of peptides has always been faced problems when administered through oral route due to presence of hydrolytic enzymes and a variety of pH system. Yoshida et al., (1992) investigated that peptides entrapped (vasopressin derivative) noisome for oral delivery showed greater stability of peptides as entrapped in pronoisome [45].

Proniosomes as carriers for haemoglobin

Moser et al., (1989) conducted the study with taking noisome as a carrier for haemoglobin within the blood and suggested that the pronoisome vesicles can be used as carrier for haemoglobin in aneamic patients as pronoisome is permeable to oxygen [46].

Proniosomes as transdermal drug delivery system

In recent time, proniosome has been received a great attention for delivering the drug substances via transdermal route as transdermal administration of drug avoids some drawbacks unlike oral route. Both hydrophilic and lipophilic drugs like: losartan potassium [47], chlorpheniramine maleate [48], levonorgestrel [35], flurbiprofen [49], ketoprofen [50], captopril [33], celecoxib [51], piroxicam [1, 52], carvediol [53], methotrexate [54], doxorubicin [55] have been found high permeation efficiency through the skin. Proniosomal preparation now has been used in cosmetics.

Conclusion

In last few decades, the thought like proniosome or proniosome derived niosome drug delivery systems have been brought a new dimension in pharmaceutical research and also extensively accepted by the researcher in targeting the particular organ or tissue destination for better treatment. It can be used as non-invasively through transdermal drug delivery system as well as oral drug delivery system. In case of vesicular system, niosomes are well accepted because it has high chemical stability as well as low cost in comparison to conventional liposomal system. Proniosome can also accommodate the wide variety of drug substances in its multi compartments structure. It has been found that niosome can be used to target organ or tissue in treatment of cancer, leishmaniasis and delivery of peptides and haemoglobin. Proniosome-derived niosome in transdermal drug delivery system is now the subject of interest and a numerous number of researches have been carried out on this subject. According to the, article, it is concluded that proniosomes and niosomes have been becoming a major delivery system in noninvasive system of drug delivery.

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