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NOVELTY OF NIOSOMAL GEL IN TDDS APPLICATION

Suma U S*[1], S. Parthiban[1], G.P. Senthil Kumar[2], T. Tamiz Mani[3]

*[1]Department of Pharmaceutics, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India.

[2]Department of Pharmaceutical Chemistry, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India.

[3]Department of Pharmacognosy, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India.

ABSTRACT

Transdermal drug delivery systems is a new approach to provide prolonged action of the drug. Recently niosome are becoming popular in the field of topical drug delivery. This niosome formulation is generally accepted by the patient due to non-toxic and non - immunogenic. Niosome are the microscopic lamellar structures composed of non-ionic surfactants and cholesterol. It includes various types of non-ionic surfactants like ester linked surfactants, alkyl ethers, tweens and spans. Niosome can be prepared by different methods includes thin film hydration, either injection emulsion method etc. The niosome gel can be prepared by using 1% carbopol gel. The prepared formulation can be evaluated for size, vesicular diameter, entrapment efficiency, *in vitro* release. Niosome can be enhanced by developing noisome gel formulation for prolonged drug release pattern. Finally this review presents that, the Tran dermal delivery via niosome gel is a suitable delivery for a better activity of drug for a long period of time.

KEYWORDS

Niosomal gel, Transdermal drug delivery system, Thin film hydration, Spans and Tweens.

Author of Correspondence:

Suma U.S.
Department of Pharmaceutics,
Bharathi College of Pharmacy,
Bharathinagara, Mandya, Karnataka, India.

Email: SumaU316 @ gmail.com

INTRODUCTON

Transdermal drug delivery systems have evolved as a successful alternative to systemic drug delivery[1]. It is a new approach to provide prolonged action of the drug with low toxicity and better patient compliances and thus reduces the side effects caused by oral route[2]. Transdermal drug delivery is defined as self - contained discrete dosage form which when applied transversally provides systemic circulation at controlled rate[3]. Dermal delivery

defines a targeting to the pathological sites within the skin with the least systemic absorption. Recently niosomes are becoming popular in the field of topical drug delivery due to its outstanding characteristics like enhancing the penetration of drugs, providing a sustained pattern of drug release and ability to carry both hydrophilic and lipophilic drugs. Niosomes in topical delivery system focusing on its clinical approach[4]. Niosomes are non - ionic surfactant based multilamellar or unilamellar vesicles in which an aqueous solutions of solute is enclosed by a membrane resulting from the organization of surfactant macromolecules as bilayer[5]. Topical applicability of niosomes was further enhanced by developing niosomal gel formulation using carbines. The release from the niosomal gel was highly prolonged when compare to conventional gel[6]. As well as the presence of other ingredients that act as skin permeation co - enhancers[7]. The niosomal gel showed a prolong drug release behaviour compare to plain gel with transdermal application[8].

ADVANTAGES[9,10]

- Provide steady delivery / blood vessels.
- Reduce systemic drug interaction.
- Improved bioavailability.
- More uniform plasma levels.
- Can minimize abuse / diversion.
- Self - administration medicament.
- It is painless and non - invasive drug delivery system.
- Longer duration of action resulting in a reduction in dosing frequency.

TYPES[11]

The various types of niosomes are described below,

i) Multi lamellar vesicles (MLV),
ii) Large unilamellar vesicles (LUV),
iii) Small unilamellar vesicles (SUV).

STRUCTURE OF NIOSOMES[12-14]

Cholesterol and Nonionic surfactants are the two major components used for the preparation of niosomes. Cholesterol provides rigidity and proper shape. The surfactants play a major role in the formation of niosomes. non-ionic surfactants like spans (span 20,40,60,85,80), tweens (tween 20,40,60,80) and brij (brij 30,35,52,58,72,76) are generally used for the preparation of niosomes.

Ether linked surfactant
Di – alkyl chain surfactant
Ester linked surfactant
Sorbian Esters
Poly - sorbets

Non-ionic surfactants

The main component in niosomal formulations is Non-ionic surfactants which possess hydrophilic head group and a hydrophobic tail. The hydrophobic moiety may consist of 1/2/3 alkyl chains (chain length is from C12-C18) or perfluro group (chain length having C10) or in certain cases a single stearyl group[15].

Cholesterol

In noisome, non-ionic surfactant is usually stabilized by addition of cholesterol. Rigidity and proper shape and conformation of the niosomes preparations can be achieved by using Cholesterol[15].

Other additives

Dicetyl phosphate (DCP) and stearyl amine (SA) are used as membrane additives which induces negative or positive charge in niosomes because they increase surface charge density and prevent vesicles flocculation, aggregation and fusion[16].

METHODS OF PREPARATION OF NIOSOMES

Niosomes can be prepared using non – ionic surfactants. Most of the experimental methods consist of the hydration of a mixture of the surfactant / lipid at elevated temperature followed by optional size reduction to obtain a colloidal dispersion. Subsequently, the unentrapped drug is separated from the entrapped drug by centrifugation, gel filtration or dialysis. The novel heating method and other well – known procedures for noisome preparation are summarized below[17].

Heating Method

This is a non-toxic, scalable and one - step method and is based on the patented procedure of Mozafari. Mixtures of non - ionic surfactant, cholesterol and / or charge inducing molecules are

added to an aqueous medium (e.g. buffer, distilled H2O, etc.). In the presence of a polyol such as glycerol. The mixture is heated while stirring (at low shear forces) until vesicles are formed[17].

Passive Trapping Techniques

This category include most of the techniques used in preparation of niosomes in which drug is incorporated during the preparation of niosomes i.e. during their formation[18].

Thin Film Hydration

All vesicles forming Components i.e. surfactant, cholesterol and charge inducers are dissolved in a volatile organic solvent in a round bottom flask. Using rotary evaporator the organic solvent is evaporated at room temperature forming a thin dry film of Dissolved components. The dried thin film is hydrated with aqueous phase with gentle agitation which leads to formation of niosomes[18].

Micro fluidization

The two phases are allowed to interact at ultra-high speed in micro channels in an interaction chamber. The high speed impingement and the energy involved leads to formation of uniform and small niosomes. This method has a high degree of reproducibility[18].

Sonication

A typical method of production of the vesicles is by Sonication of solution was introduced. In this method an aliquot of drug solution in buffer is added to the surfactant / cholesterol mixture in a 10- ml glass vial. The mixture is probe sonicated at 60°C for 3 minutes using a sonicator with a titanium probe to yield Niosomes[19].

Multiple membrane extrusion method

Mixture of surfactant, cholesterol and dicetyl phosphate in chloroform is made into thin film by evaporation. The film is hydrated with aqueous drug solution and the resultant suspension extruded through polycarbonate membranes, which are placed in series for up to 8 passages. It is a good method for controlling noisome size.20.

Injection Method

In this method, add a solution of surfactant dissolved in diethyl ether slowly into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14 - gauge needle into an aqueous solution of material. The vaporization of ether results in the formation of single layered vesicles[21].

Ether injection method

A solution of surfactant mixture is prepared first and then slowly introduced into warm water maintained at 60°C. The surfactant mixture in ether is injected through 14- gauge needle into an aqueous solution of material. Single layered vesicles are formed by the vaporization of ether. The vesicles of diameter range from 50 to 1000 nm are obtained depending upon the conditions used. The small amount of ether is often still present in the vesicle suspension and is often difficult to remove that is the major disadvantage of this method[22].

METHOD OF PREPARATION OF NIOSOMAL GEL

For the formulation of niosomal gel, the gel base was prepared by dispersing 1% w/w carbopol 940 in a mixture of water and glycerol (7:3), the dispersion is then neutralized and made viscous by addition of sufficient amount[23].

Preparation of carbopol gel

Sufficient quantity of Carbopol 934 (1% w/w) was weighed and sprinkled onto warm distilled water with continuous stirring. The dispersion was allowed to hydrate for 1-2 hours. Other ingredients like Propylene Glycol (10 % w/w) and Glycerol (30 % w/w) were added subsequently to the aqueous dispersion with continuous stirring. A plain drug gel was prepared by adding required quantity of drug (2 % w/w) and dispersed properly. The dispersion was neutralized to pH 6 using 1 % w/v of Sodium Hydroxide solution and the final weight was adjusted with distilled water. The gel was sonicated for 30 minutes on bath sonicator and kept overnight to remove air bubbles. Niosomal gel was prepared by following the same procedure and adding niosomal cake containing an equivalent amount of drug instead of plain drug[24].

CHARACTERIZATION OF NIOSOMES

Vesicle structure and shape can be characterized by various types of microscopy such as optical freeze fracture electron, surface electron, scanning electron, negative staining transmission electron, cryo-electron, fluorescence and confo-cal[2].

Size and vesicle charge

Size and charge of vesicles have a significant effect on their stability and drug encapsulation. Size and charge can be assessed using a multifunctional zeta potential analyzer where size of vesicles is the result of repulsion forces between the bilayers and the entrapped drug[25, 26].

Entrapment efficiency

After preparing niosomal dispersion, unentrapped drug is prepared by dialysis, centrifugation, or gel filtration and the drug remained entrapped in noisome is determined by complete vesicle disruption[27].

Entrapment efficiency (EF) = (Amount entrapped total amount) ×100

Number of lamellae

This is determined by using nuclear magnetic resonance (NMR) spectroscopy, small angle X-ray scattering and electron microscopy[28].

Membrane rigidity

Membrane rigidity can be measured by means of mobility of fluorescence probe as a function of temperature[29].

***In - vitro* release**

A method of *in vitro* release study includes the use of dialysis tubing. A dialysis sac is washed and soaked in distilled water. The vesicle suspension is pipette into a bag made up of the tubing and sealed. The bag containing in the vesicles is placed in 200ml of buffer solution in 250 ml beaker with constant stirring at 25°C or 37°C. At various time intervals, the buffer is analyzed for the drug content by an appropriate assay method[30.]

CHARACTERIZATION OF NIOSOMAL GEL[31]

Consistency and clarity

After the preparation , the gel formulation were visually inspected by naked eyes.

PH determination

The pH of the gel formulation was measured using digital pH meter. The gel formulations were diluted in ratio 1:25 using distilled water. Standard buffer solution of pH 4, 7 and 10 were used for calibration of pH meter it is tested in triplicate to obtain mean pH value. The diluted gel was in contact pH electrode for 10 min to allow the pH values to stabilize.

Assay and content drug uniformity

Fixed quantity of the gel samples were collected from different sites of transdermal patch and accurately weighed into a 10 ml volumetric flask each. Around 8 ml receptor medium was added and flask was shaken vigorously to disperse the gel followed by sonication for 10 min for complete extraction of the drug. Then prepared stock solutions were filtered, diluted and analyzed by UV spectroscopy.

Viscosity

The viscosity of gel formulation was determined by Brookfield viscometer using spindle no.7 at temperature of 30°C.

Skin irritation test

It was performed to evaluate the deleterious effect of the transdermal patch that may have a on the skin when applied on to the skin. The niosomal gel formulation enhances the penetration of the drug in epidermal layer but not through the skin layers into the diffusion medium.

NIOSOME AS A SKIN DELIVERY

Several mechanisms have been suggested to describe the ability of niosomes in Transdermal and dermal drug delivery:

- Niosomes diffuse from the *stratum corneum* layer of skin as a whole
- Re-formation of noisome vesicles
- Interaction with *stratum corneum* with aggregation, fusion, and adhesion to the cell surface which causes a high thermodynamic activity gradient of the drug at the vesicle-*stratum corneum* surface.

- Modification of *stratum corneum* structure which results in the intercellular lipid barrier of *stratum corneum* looser and more permeable.
- Niosomes constructed from a new non-ionic surfactant alpha, omega-hexadecyl-bis-(1-aza-18-crown-6) (bola-surfactant), span 80 and cholesterol show significantly improved percutaneous permeation of ammonium glycyrrhizin ate. Niosomes constructed from cholesterol, span 60 and dicetyl phosphate were effective in increasing skin permeation of frusemide across mouse skin as compared to conventional formulation.
- The migration of cyclosporine A from cyclosporin glyceryl dilaurate/C16EO10 /cholesterol niosomes into the deeper skin strata has also been studied in vitro and it was found that factors such as dosing volume in non-occluded conditions affected the rate of uptake with smaller dose volumes giving rise to an increased uptake of the drug into deeper skin strata. The transdermal drug delivery with niosomes appears to be a promising carrier for hydrophobic and amphiphilic drug molecules and would require that the dose be applied in high concentrations and within niosomes prepared from low phase transition surfactant mixtures[4,32].

APPLICATION

Transferral delivery of drugs by niosomes, an increase in the penetration rate has been achieved by transdermal delivery of drug incorporated in niosomes as slow penetration of drug through skin is the major drawback of transdermal route of delivery for other dosage forms[33]. **M.A. Lingan *et al.*** prepared the topical gel containing clobetasol propionate niosomes and prevent its side effects and he reported that it acts as a suitable topical drug delivery system to prolong the duration of action[34]. **Ankusha Gupta *et al.*** formulated the topical niosomal gel containing combination of benzoyl peroxide and tretinoin and reported that the niosomal gel was more efficacious than the antiacne creams[35]. **Saxena *et al.*** demonstrated that the encapsulation of Roxithromycin into niosomal gel formulation improves Invitro drug release– and therapeutic response[36]. **Ketul K *et al.*** formulated the niosomal gel for enhanced transdermal lopinavir delivery and suggested that the niosomal gel holds a great potential of being utilized as novel, vehicle for transdermal lopinavir delivery[37]. **Mohamed a *et al.*** formulated the topical niosomal gel of baclofen and his result suggested that, the niosomal delivery of baclofen in carbopol gel base acts a suitable topical drug delivery system[38]. **P.U. Mohamed Firthouse *et al.*** investigated the feasibility of noisome as a transdermal drug delivery system for miconazole and reported that the formulation with1:1 cholesterol surfactant ratio showed 92.10% drug release in 24 hr[39]. **Singla Kapil *et al.*** Prepared the lornoxicam niosomal gel by thin film hydration and reported that physicochemical characterization and invitro permeation studies of the prepared vesicles were promising to formulate transdermal drug delivery system[40]**. K. Srikanth *et al.*** developed the niosomal nystatin gel for transdermal administration and reported that, the *In vitro* and *ex vivo* drug release studies of niosomal gel shows niosomal gel sustains the drug release than the marketed gel[41]. **Sidramappa B Shirsand *et al***. concluded that encapsulating clotrimazole in non-ionic surfactant vesicles would provide better patient compliance by achieving prolonged release of the drug to the dermis with improved efficacy [42]. **Modi Kushal A *et al.*** concluded that, the Acyclovir will be available for longer time at the site of infection of skin and hence total therapy time can be reduced to the much extent when given topically in niosomal dosage form[43]. **PK Lakshmi *et al***. concluded that niosomal methotrexate gel is more efficacious than placebo and marketed methotrexate gel[44]. **SB Shirs and *et al***. reported that, the gel formulation containing niosomes loaded with Ketoconazole showed prolonged action than formulations containing Ketoconazole in non-niosomal form and it can be developed successfully to improve the antifungal activity[45].

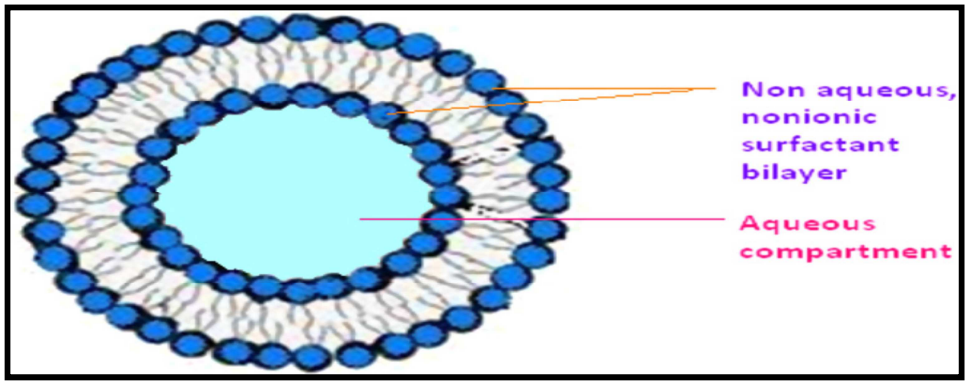

Figure No.1: Structure of a Non- ionic surfactant vesicle (noisome)

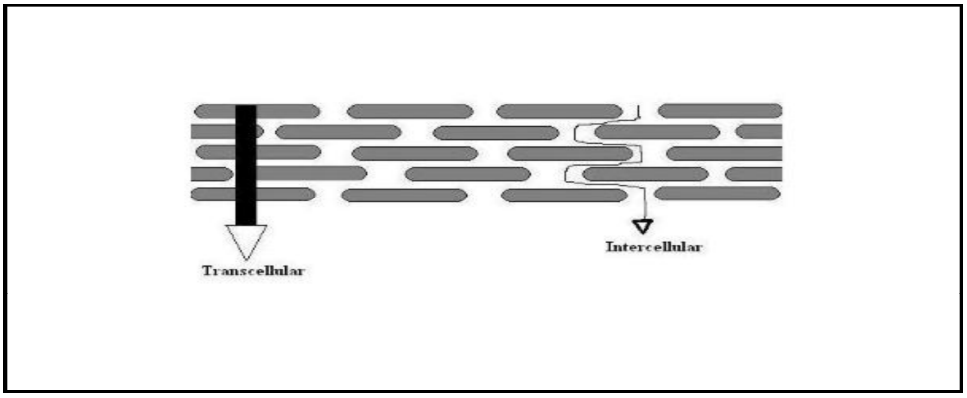

Figure No.2: A schematic representation of the skin showing the trans cellular and intercellular routes of penetration

CONCLUSION

Niosomal drug delivery systems have been demonstrated to be promising controlled drug delivery systems for percutaneous administration. Niosomes offer successful drug localization in skin which is relatively non - toxic and stable. Many topical drugs may be developed using niosomal systems. Hence this review work concluded that the Transdermal delivery of drug via niosomal gel preparation provide a better means of delivery in terms of enhanced permeation of drug from the skin to achieve better activity for long period of time in a rate controlled manner.

CONFLICT OF INTEREST

We declare that we have no conflict of interest.

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