A Review on Topical Drug Delivery System: Proniosomal Gel

Sunil Kumar[1], Dr. karunakar shukla[2], Dr. Saurabh jain[3], [4]Alka srivastava
[1]*Research schlor, Department of Pharmaceutics, Dr. APJ Abdul kalam University Indore M.P*
[2]*Principal, Instiute of pharmacy, Dr. APJ Abdul kalam University Indore M.P*
[3]*Associate professor, Dr. APJ Abdul kalam University Indore M.P*
[4]*Assistant Professor, maharishi university of information technology*

Abstract **- The transdermal route of drug delivery has a number of advantages in terms of drug administration in both local and systemic therapy. Proniosomes, which are manufactured in dry form and then hydrated in hot water to create niosomes, offer a promising alternative for drug delivery via the transdermal route. However, when compared to other biological membranes, skin is well known for its effective barrier qualities. Dermal delivery is an alternative channel because of the skin's limited permeability, while dermal delivery is an alternative route. Poor bioavailability, variable absorption, and pharmacokinetic alterations are common side effects of newer lipophilic medicines. This proniosomal gel is a compact semi-solid liquid crystalline (gel) made up of non-ionic surfactants that may be easily created by dissolving the surfactant in the smallest amount of appropriate solvent, aqueous phase, and phosphate buffer. Topical application of gel in an occlusive environment, during which they are transformed to nisomes due to hydration by water in the skin. Proniosomal gels are usually semisolid gels with a transparent, translucent, or whitish texture, which keeps them physically stable throughout storage and transportation. The manufacture, formulation, assessment, and application of proniosome gel as a drug delivery carrier are all covered in this review.**

Index Terms **- Topical drug delivery, Coacervation phase separation, Vesicular drug delivery, Proniosomal gel, Non-ionic surfactants.**

INTRODUCTION

Gastric drug/enzyme instability and first-pass metabolism are issues with oral solid dose formulations. Other issues with the oral route include an unpleasant taste, odour, and colour. The transdermal route of drug delivery has a number of advantages in terms of drug administration in both local and systemic therapy. However, when compared to other biological membranes, skin is well known for its effective barrier qualities. Because of its limited permeability, the skin is only a small drug entry point. Vesicular drug delivery may be advantageous because vesicles tend to fuse and stick to the cell surface; this is thought to raise the drug's thermodynamic activity gradient at the vesicle-stratum corneum contact, resulting in increased penetration rate. Understands nature's intrinsic inclination, birds, and animals have continued to struggle with the formation of mesapatonia, practising pharmacist treatment, and sharing his knowledge for the benefit of those who have suffered. For illness, tablets were employed, with several routes of administration accessible for the sequential delivery of prescribed dosage forms [1]. The characterisation of the active ingredient is crucial to the development of a formulation. Oral administration is the most popular method, with a high level of patient compliance. However, bioavailability is still a work in progress, with poor solubility of the drug candidate leading to limited absorption [2]. The biggest issue found with the formulation design of new chemical moiety is less water solubility [3]. According to recent study on the production of hydrophobic active pharmacological components [4], roughly 40% of new medications have low water solubility [5]. Particle size reduction, nano ionisation, cosolvency, hydrotropy, pH adjustment, sono crystallisation, supercritical fluid process, solid dispersion, inclusion complexation, self-emulsifying or self-micro emulsifying systems, and liquisolid methods have all been used to improve solubility and dissolution rates of poorly water-soluble drugs [6]. a variety of One such technique is drug encapsulation in vesicular structures, and a variety of vesicular drug delivery

systems, such as liposomes, niosomes, transfersomes, and pharmacosomes, have been created [7]. Transdermal dose forms are gaining popularity as an alternative to traditional dosage formulations due to their unique benefits. Improved bioavailability, regulated absorption, extra consistent plasma levels, painless application with less side effects [8]. However, the advantages of the transdermal route are offset by the shortcomings of their formulations, such as ointments, creams, and lotions, which have a number of drawbacks, including sticky texture, poor spreadability, and concerns regarding stability.

Because of its simplicity and accessibility, topical administration is the most popular method for delivering medicinal substances locally. Vesicular drug delivery systems are a revolutionary way to improve the bioavailability of the encapsulated medicine while offering more benefits than traditional dose forms. Liposomes were the first in this sort of delivery system, however they were not very effective due to a number of flaws [10].

The goal of creating a therapeutic system is to achieve an optimal concentration of a medicine at its site of action for a reasonable amount of time [9]. Niosomes, also known as non-ionic surfactant vesicles, are a microscopic lamellar structure in aqueous fluids that consists of spherical, uni- or multi-lamellar, and polyhedral vesicles with sizes ranging from 10–1000 nm [11]. Butnoisomes have physicochemical stability issues when storing dispersion, such as aggregation, fusion, drug leakage, or hydrolysis of the active chemicals, which raises questions about their use [12]. By retaining the physical and chemical integrity of vesicles, proniosomes were manufactured as a dry powder for reconstitution before use [13]. Proniosomes were created as gel-like concentrated niosomes suited for topical use for transdermal administration [14]. Proniosomes are a semisolid, liquid crystal (gel) result of a nonionic surfactant that transforms to niosomes when hydrated [15,16]. When proniosomes are placed to the skin surface, they change into niosomes as a result of the skin's moisture, creating an occlusive situation and the potential for medication delivery via the transdermal route.

FORMULATION INGREDIENTS

Phospholipids and non-ionic surfactants in proniosomes can operate as penetration enhancers, since some phospholipids have been shown to be able to fluidize and diffuse through the stratum corneum lipid bilayers [17], whilst cholesterol gives the vesicles stability and permeability.

Surfactants

Non-ionic surfactants were primarily associated with the production of proniosomal gel. Solubilizers, wetting agents, emulsifiers, and permeability enhancers are all used [18]. Based on the hydrophile-lipophile balance (HLB) values of the available surfactants, which are principally divided into w/o emulsifying agent (HLB 3–8) and o/w emulsifying agent (HLB 8–16) [19], an HLB value of 4–8 would usually result in vesicles with high compatibility. Table 1 [20] lists the most frequent nonionic amphiphiles utilised in proniosome formulations.

Cholesterol

It is an important component in the design of proniosomes that offers the vesicles stability and penetrability. The amount of cholesterol entrapped determines the entrapment efficiency (EE). Cholesterol may aid bilayer construction; vesicles cannot be formed without cholesterol, and larger cholesterol contents reduce the time necessary for niosome assembly. It avoids accumulation by including molecules that stabilise the system, preventing the formation of an aggregate due to repulsive steric or electrostatic interactions [23].

Lecithin

- Mostly utilised as membrane stabilisers are two types of lecithin: soya lecithin and egg lecithin [21]. Soya lecithin is derived from soya beans, while egg lecithin is derived from egg yolk. The following materials were used in the project.
- Soya lecithin.
- L-α-egg phosphatidyl choline.
- 1-2-dimyristoyl-snglycero-3-phosphocholine.
- 1-2-distearoyl-snglycero-3phosphocholine.
- Dipalmitoylphosphatidylcholine [22].

Carrier material

a. The inclusion of maltodextrin in the creation of proniosomes allowed for greater flexibility in the ratio of surfactant and other components that might be used [25]. Furthermore, it improves the surface area, resulting in more efficient loading. The

carriers should be non-toxic, free-flowing, and have a low solubility in the loaded mixed solution but a high solubility in water for easy hydration. Sorbitol, mannitol, glucose, lactose, and sucrose stearate are commonly used carriers [15]; commonly used carriers are listed below [26].

b. Maltodextrin.
c. Sorbitol.
d. Spray dried lactose.
e. Glucose monohydrate.
f. Lactose monohydrate.
g. Sucrose stearate

Solvent and aqueous phase

Alcohol has a significant impact on the size of vesicles and the rate of drug absorption in a proniosomal formulation. Ethanol,propanol, butanol, isopropanol, isopropanol, isopropanol, The aqueous phase in the preparation of proniosomes is phosphate buffer 7.4, 0.1 percent glycerol, and hot water [24].

Drug

The drug selection criteria could be based on the following assumptions.

1. The low aqueous solubility of drugs.
2. High dosage frequency of drugs.
3. Short half-life.
4. Controlled drug delivery suitable drugs.
5. Drugs are having more adverse effects [27].

Advantages

Unlike other vesicular systems, proniosomes were simple to create and did not require particular storage conditions [28].

- Exhibits a high EE.
- They have the ability to transport both hydrophilic and hydrophobic medicines.
- Drug targeting for controlled release is widely employed
- Handling, storage, and transportation are all simple.

Classification of proniosomes

In general, proniosomes were divided into the following types [29].

- Semi-solid liquid crystal gel.
- Dry granular powder Fig. 1.

Methods of preparation of proniosomal gel

- Coacervation phase separation.
- Slow spray coating method.
- Slurry method.

Coacervation phase separation

Proniosomal formulae were made according to a method described by Alsarra et al. [30] with minor changes, employing various non-ionic surfactants, lecithin, and cholesterol. In a clean and dry wide-mouth glass tube, appropriate amounts of proniosomal components mixed with the medication were mixed with 2.5 ml of absolute ethanol. After thoroughly mixing all of the materials, the open end of the glass tube was sealed with a lid to prevent solvent loss and warmed in a water bath at 65 3°C for 5 minutes, until the surfactants were completely dissolved. Then, 1.6 mL of pH 7.4 phosphate buffer was added, and the water bath was heated for another 2 minutes until a clear solution was obtained. The dispersion was allowed to cool to ambient temperature before being transformed to a proniosomal gel [31,32].

Slurry method

carrier material to a 250-ml flask and the entire volume of surfactant solution was added the flask to form the slurry. If the surfactant solution volume is less, then additional organic solvent can get slurry. The flask was attached to a rotary evaporator was applied until the free flowing. The flask was removed from the evaporator and kept under vacuum overnight. The proniosome powder was stored in sealed containers at 4°C. The time required to produce proniosomes is independent of the ratio of surfactant solution to the carrier material and appears to be scalable [25].

Slow spray - coating method

This approach includes spraying surfactant in an organic solvent onto carrier material and then evaporating the solvent to make proniosomes. Because the carrier is soluble in the organic solvent, the operation is repeated until the desired result is obtained. The surfactant coating on the carrier is very thin, and as the carrier dissolves, the hydration of this coating permits multilamellar to form [36,37]. The generated noise is quite comparable to that produced by traditional methods, with a more uniform size distribution. This formulation is thought to provide hydrolysis for hydrophobic drug formulation [38].

EVALUATION OF PRONIOSOMES

Percentage Entrapment Efficiency

Proniosomal gel (0.2 g) was reconstituted in a glass tube with 10 ml of pH 7.4 phosphate buffer. The aqueous suspension was sonicated for 30 minutes in a sonicator bath. By centrifuging at 9000 rpm for 45 minutes at 4°C, the naproxen-containing niosomes were separated from the untrapped substance. The medication concentration in the resultant solution was determined using an ultraviolet (UV) spectrophotometer set to a certain wavelength. The following equation was used to compute the percentage of medication encapsulation:

EE%=[(Ct–Cf)/Ct]×100.

Where Ct is the concentration of a total drug and Cf is the concentration of a free drug [15,39].

Vesicle size and zeta potential analysis

The mean vesicle size, size distribution, and zeta potential were determined using a Dynamic Light Scattering technique by Malvern- Zetasizer (Nano ZS90). In a glass tube, 0.2 g proniosome gel was diluted with 10 ml of pH 7.4 phosphate buffer. The vesicle measurements were done at a temperature of 25±0.5°C. The polydispersity index (PI) was determined as a measure of homogeneity. PI is obtained as:

PI=(SD/vesicle size).

Small values of PI (<0.1) indicate a homogeneous population, while PI values >0.3 indicate high heterogeneity [40].

MICROSCOPICAL EXAMINATION

Optical microscope

A few drops of the generated niosomal dispersion were distributed on a glass slide and analysed for the presence of insoluble drug crystals using an ordinary light microscope with various magnification levels (10 and 40). A digital camera was used to take photomicrographs [40].

Scanning electron microscopy (SEM)

SEM was used to examine the form, surface features, and size of the proniosomes. The morphological differences in shape and surface properties of the formed proniosome derived noisome of formulae with varying cholesterol contents were investigated using a scanning electron microscope in an attempt to highlight the role of cholesterol in vesicle formation. 0.2 g proniosome gel was diluted with 10 ml pH 7.4 phosphate buffer in a glass tube; the dispersion was sprinkled and fixed on a SEM holder with double-sided adhesive tape; the dispersion was coated with a layer of gold of 150 for 2 min using a Sputter Coater (Edwards, S-150A, England) working in a vacuum of (3101 atm) of Argon gas [41].\

DSC

Taking thermal parameters into account, this method aids in the investigation of probable interactions between medication and vesicle constituents. Differential scanning colorimetry (DSC) with a diamond (DSC) was used to assess the thermal characteristics of the pure medication and the formulation. The analysis was carried out at a rate of 50°C min-1 throughout a temperature range of 50°C to 200°C with a nitrogen flow rate of 25 ml/min. DSC analysis was performed on samples of 4 mg of each drug, surfactants, empty and drug-loaded proniosomes-derived niosomes, and samples of 4 mg of each drug, surfactants, and empty and drug-loaded proniosomes-derived niosomes. The weighed sample was then heated at a rate of 10°C/min from ambient temperature to 300°C [42].

Fourier transforms infrared spectroscopy (FTIR)

Drug powder was compressed into a pellet along with KBr using a hydraulic press. The IR spectrum of drug and final optimized formulations were recorded in the wavenumber region of 4000– 400 cm^{-1} on FTIR [42].

IN VITRO RELEASE

The vertical glass Franz diffusion cells with a diffusional surface area of 1.13 cm2 and a receptor compartment of 10 ml capacity were used in the release investigation [43]. Before cutting into sufficient pieces, the cellulose dialysis membrane was soaked in distilled water overnight. This soaking was done to ensure that the membrane was completely swollen and that the pore diameter remained consistent during the experiment. After that, the membrane was placed between the donor and receptor compartments, and the receptor compartment was filled with pH 7.4 phosphate buffer.

The diffusion cells were incubated into a thermostatically controlled circulator water bath. The temperature of the receptor compartment was maintained at 37±0.5°C, and the receiver medium was continuously stirred to prevent any boundary layer effects. Weight amount of proniosomal gels were loaded into the donor compartments; then it was covered with an aluminum foil to prevent evaporation. At predetermined time intervals, namely 1, 2, 3, 4, 6, 8, 12, 18, and 24 h, samples of 1 ml were taken from the receptor compartment and replaced immediately by fresh buffer solution; to maintain the "sink" conditions constantly and a constant volume as well. The samples were then assayed spectrophotometrically.

All of the release tests were carried out in triplicate. The time was plotted against the cumulative percentage drug release. The kinetic treatment of the collected release data was done using the zero, first, Hixson Crowell, and Higuchi diffusion models. In each case, the correlation coefficient (r) and the order of release pattern were established.

RATE OF SPONTANEITY (HYDRATION)

The number of niosomes generated after 15 minutes of hydration of proniosomes is referred to as the spontaneity of niosome creation [44]. Proniosomal gel (10 mg) was evenly distributed in the bottom of a tiny, stoppered glass tube. 1 mL of pH 7.4 phosphate buffer was added to the test tube's walls and set aside without being agitated. A drop of hydrated material was removed after 15 minutes and placed in Neubauer's chamber to count the quantity of niosomes eluted from a proniosomal gel.

PHYSICAL STABILITY

The change in EE after storage was used to detect vesicle aggregation or fusion as a function of temperature [45]. The vesicles were preserved for three months in glass vials at ambient temperature (37°C) or in the refrigerator (4–8°C). In an improved formulation, the retention of entrapped medication and the mean particle size were assessed after preparation and subsequently after 1, 2, and 3 months of storage. The samples were also examined under an optical microscope at the end of each month for any signs of drug crystallisation. The stability of a formulation was determined by its capacity to maintain its original EE for a period of three months. At each time interval, a stable formulation was defined as one with a high EE (>60%) and a high drug retention value (>90%).

Drug retained in proniosomes=(Entrapped drug after storage/ entrapped drug before storage) ×100.

Concise evidence of published proniosomal gel formulations and its influence on pharmacology

CONCLUSION AND FUTURE PROSPECT

Proniosomal gel has a variety of ingredients, and selecting them necessitates understanding of their qualities, which differ from one another. Surfactant, lecithin, cholesterol, and the function of manufacturing method have distinct advantages that influence the quality of the final formulation. Thus, the development of a stable proniosomal gel is solely dependent on the appropriate ingredients and methodology used in the preparation of the proniosomal gel. The proniosomal gel preparation is more comfortable, stable, and widely used in drug targeting for controlled release of both hydrophilic and hydrophobic drugs. Proniosomes' gel characteristic allows for improved skin penetration and physicochemical qualities. Because cholesterol provides stability and permeability to the vesicles by preventing aggregation, fusion, drug leakage, and hydrolysis of the active chemicals, proniosomal gel formulations are a promising new transdermal dosage form for treating dermatological and other systemic skin conditions. Proniosomal gel is applied topically to treat the condition.

AUTHORS' CONTRIBUTION

Data collecting, information, writing, and critical evaluation were all equally important in the development of the document's structure.

CONFLICTS OF INTEREST

There are no conflicts of interest declared by the authors.

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