Niosomal Gels for Use in Skin Treatments

Fatemeh Kashani-Asadi-Jafari [1] - Afra Hadjizadeh [2] – Shokoofe Rostampoor [3]
[1,2,3] Biomedical Engineering, Amirkabir University of Technology, Tehran 159163-4311, Iran

ABSTRACT

Human skin protects the body as a barrier against external attacks by microorganisms and other environmental factors. Drug release through the skin does not pose the risks of oral and injectable drug delivery, and the drug does not pass through paths with different pH, so there are no problems in the breakdown and metabolism of the drug in the body, and there is targeted delivery of the drug. There are different carriers for this type of release. However, today niosomes have received much attention because of their many benefits, including biodegradability, biocompatibility, and the ability to encapsulate large amounts of drug material in small volumes of vesicles, greater patient satisfaction, and greater effectiveness. Nevertheless, the physical stability of niosomes is a significant obstacle that limits their application to drug delivery systems. In order to reduce the rapid leakage of encapsulated drugs from the niosomes or minimize the explosive release observed in them, the niosomes are placed in a bed. Gels are suitable substrates for niosomes to improve release; therefore, this article reviews the reports of preparation and evaluation methods of gels containing niosome, and comparing gels containing niosome with gels without niosome. The results showed that higher viscosity, better penetration, more skin retention, and slower release were the characteristics of niosome-containing gels compared to niosome-free gels.

Keywords: Skin, Niosome, Gel.

1. INTRODUCTION

Skin is the largest organ in the human body, covering the entire body and protecting the body from external attacks by microorganisms and other environmental factors, such as heat, chemicals and toxins, and water loss. Since the skin is most exposed to the environment, the risk of damage and local skin diseases is very high [1].

A gel is a semi-solid substance that can be soft and weak to hard and firm [2], [3]. Gels are crosslinking systems that do not show any current in stable conditions [4]. Gels are primarily liquid, but because of their crosslinked three-dimensional network, they behave like solids, and the crosslinks can give the gel a strong structure. Thus, gels are liquid molecules dispersed in a solid medium [5].

Niosomes are carriers with microscopic layered structures composed of nonionic surfactants and cholesterol. Niosomes have an amphiphilic bilayer structure. Hydrophilic drugs can be loaded in the polar part, which is outside and inside the vesicles, and in the non-polar part, which is between the two layers, hydrophobic drugs can be trapped [6].

Drug release through the skin does not pose the risks of oral and injectable drug delivery because drugs do not pass through paths with different pH. As a result, there is no breakdown and metabolism of the drug, and there is targeted drug delivery [1].

In dermal delivery, drugs are applied directly to the target site, which leads to an increase in the local concentration of drugs and a decrease in the systemic concentration of the drug [7].

Topical medication has been used for a long time and has had different effects on different layers of the skin (skin surface, epidermis, dermis, and hypodermis). However, conventional topical methods have faced limitations such as low penetration (due to the stratum corneum layer, the outermost layer of the skin, which acts as a barrier) and absorption into the systemic circulation. Release in the dermis is targeted drug delivery to damaged areas of the skin with minimal systemic absorption. Furthermore, since the drug concentration in the local actions is vital for treating skin diseases to improve therapeutic efficiency and reduce side effects, this method is essential [6]. For this type of release, there are different carriers that, because of the many benefits of niosomes in targeted drug delivery, we decided to investigate them. The gels also help the better niosome penetration, increase their longevity on the skin's surface, and provide slower release.

Some medications cause burns, allergies, or skin irritations, which the use of gels reduces these cases. Furthermore, since one cannot apply the niosome suspension directly to the skin, using a gel bed to commercialize the niosomes seems appropriate.

2. LIPID-BASED VESICULAR SYSTEM

Lipid vesicles are experimental models of biomembranes that have been successfully developed as carriers for drug delivery. The advantage of using lipid vesicles for topical applications is the hydrophobic nature of the vesicle wall, which can be helpful for water-insoluble substances. They increase penetration by having hydrophobic properties. In addition, lipid vesicular systems do not release the incorporated molecule immediately and can act as a local reservoir system. In addition to these benefits, vesicular systems reduce the cost of treatment by increasing the bioavailability of drugs with low solubility. Also, instability and insolubility, and rapid destruction of the drug can be solved [7]. Niosomes are innovative vesicular delivery systems used for sustained, controlled, and targeted drug delivery. Liposomes were the first vesicular drug delivery systems, but they have disadvantages such as toxicity, high cost, and stability problems at different pHs. Due to the defects of liposomes, research interest shifted to niosomes. Niosomes can be used to deliver drugs for skin cancer, psoriasis, vitiligo, and acne [6], [8].

3. NIOSOME

Niosomes are generally prepared using single-chain nonionic surfactants using thin-film hydration and form a bilayer structure [9]. Nonionic surfactants have hydrophilic heads and hydrophobic alkyl chains. These thermodynamically stable bilayer structures are formed when surfactants and cholesterol are mixed in the appropriate ratios, and the temperature must be above the temperature of the gel-to-liquid phase transition [8]. Thus, niosomes can be used to load both polar and non-polar compounds [9].

Some of the advantages of niosomes over conventional drug delivery systems include the followings:

1. Compared to liposomes, niosomes have higher chemical stability and longer shelf life.
2. Due to the presence of a functional group on the hydrophilic head, the surface of the niosomes can be easily formed and modified.
3. Since niosomes are uncharged, they have low toxicity and high compatibility.
4. Niosomes do not initiate immune reactions.
5. Niosomes can improve drug bioavailability by increasing physical and biological stability [8], [10], [11].

4. SUBSTRATE USED FOR TOPICAL DRUG RELEASE

The physical stability of niosomes is a significant barrier that limits their application to drug delivery systems. In order to reduce the rapid leakage of the encapsulated drug from the niosomes or minimize their explosive release, the niosomes are placed in a bed [12]. In topical drug release, various substrates are used to incorporate formulations in them, which include the followings **Fig.1**:

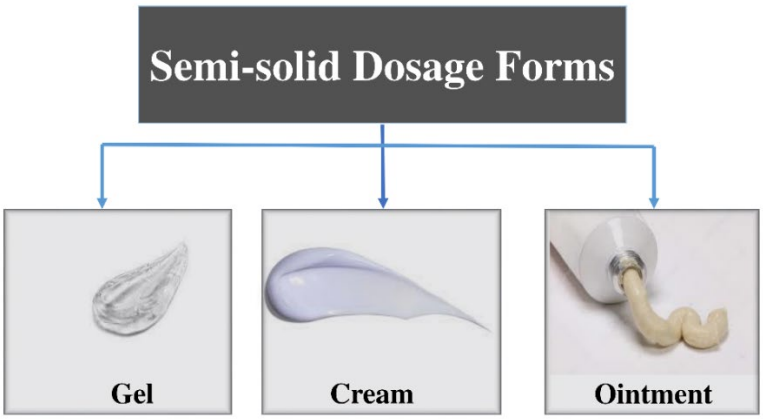

Fig. 1. *Schematics of the substrate of semi-solid dosage forms.*

4.1 Semi-solid topical dosage form

4.1.1 Ointment

An ointment is a semi-solid, homogeneous, and oily viscous formulation of dissolved or dispersed drugs [13]. In ointments, certain aqueous solvents are usually mixed with oily solvents [14]. Ointment bases improve drug flow from the skin by removing the occlusion properties of the stratum corneum. In addition, it affects the drug dissolution in the skin and the drug distribution from the ointment to the skin and, as a result, improves the local drug bioavailability. Nevertheless, their main problem is that patients do not prefer them because of their fat [13]. In an article on the treatment of semi-thick deep burns, liposomes containing retinoic acid and cationic liposomes containing epidermal growth factor were inserted into the ointment. They observed that the resulting formulation showed a high loading percentage and sustained drug release and treated the burn [15].

4.1.2 Cream

It is a semi-solid emulsion formulation for application on the skin or mucous membranes. Water-in-oil emulsion type Creams are low in fat and have an excellent spreadability compared to ointments, while oil-in-water emulsion creams are easily rubbed on the skin and easily removed by water [13]. In an article on the treatment of melasma, liposomes containing 4-N-butyl resorcinol 0.1% were encapsulated in cream and found that the resulting formulation had a more significant effect than the carrier alone for the treatment of melasma [16].

4.1.3 Gel

Gels essentially contain a liquid solvent with solid matrix components [1]. Gels do not require oil or fat to thicken and are more dependent on alcoholic or aqueous solvents. The skin does not absorb the gels as much as the oily formulations, and for this reason, they are suitable for conditions that require low absorption, such as acne and psoriasis [14].

Semi-solid formulations most commonly used for topical drug delivery include gels, creams, and ointments [17]. Creams, lotions, and gels are semi-solid substrates commonly used for niosomes. Some of the essential advantages of gel formulations over other semi-solid dosage forms include the followings:

1. They have fewer stability problems in the long run.
2. Can be used for both hydrophilic and hydrophobic drugs [18].
3. Gels have better potential as a carrier than topical ointments for topical application because they are non-sticky, require low energy during formation, are stable, and are acceptable.
4. Topical gel formulation provides a convenient release system for drugs; because they are less oily and can be easily removed from the skin [17].
5. Niosomal gels can provide a reservoir of drugs within the stratum corneum for sustained release, leading to a considerable accumulation of drugs within the dermis and epidermis. The gel can also improve the penetration of the drug through the stratum corneum due to the obstructive effects of the gel formulation,

improve skin hydration, and subsequently increase the absorption and penetration of the drug through the skin [19].

Due to the many benefits of gels in topical applications, in this study, we decided to investigate gels and gels containing niosomes **Fig. 2**.

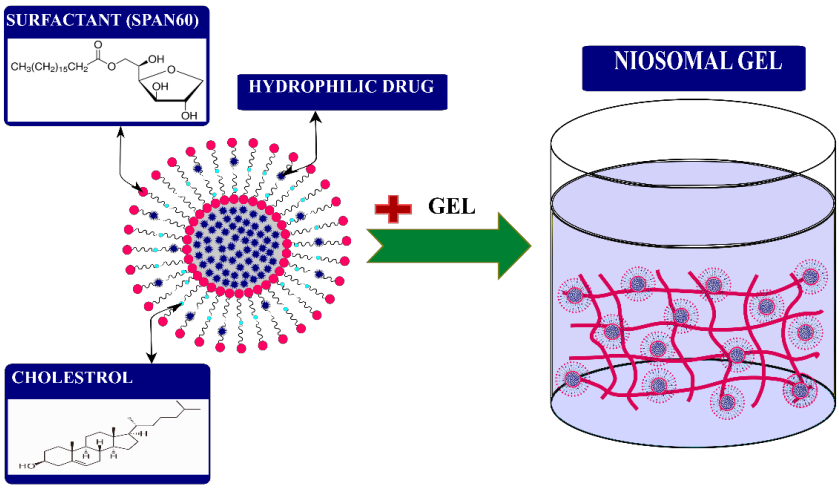

Fig. 2. *Schematic of niosome added into gels.*

5. STRUCTURE OF GELS

A gel contains a natural or synthetic polymer that forms a three-dimensional matrix throughout a distribution medium or hydrophobic fluid. After applying the gel to the skin, the liquid evaporates, and the encapsulated drug is left in a thin film of a gel matrix that physically covers the skin. The presence of a network formed by the entanglement of the gelling agent particles causes the gel to harden. The properties of the particles and the type of bonds determine the structure of the network and the properties of the gel [17]. Gels are formed by adding a gelling agent. The gelling agent is uniformly distributed among a dispersing medium or solvent and forms a three-dimensional matrix as a gel. The polymer in the gels acts as the backbone of the gel matrix. The polymer network gives the gel structural strength and reduces the penetration of large molecules, thus making storage possible. Gels are formed by balancing the polymer with the solvent. At a critical concentration, also called the gel point, the gel forms. The gel cannot form below the gel point, while the viscosity increases significantly above this point. The gel point can be determined based on the hydrophilic and lipophilic balance of the polymer, the interaction of the solvent and the polymer, the molecular weight of the polymer, and the flexibility of the polymer chain . Gels can be reversible or irreversible, depending on the type of bond. Reversible gels generally have hydrogen bonds, while irreversible gels usually have covalent bonds. A gel can be a single system without apparent boundaries or a two-phase system with separate particles [18].

6. NIOSOMAL GELS

The combination of hydrogels and niosomes improves the controlled release of drugs to treat skin diseases [1]. It is believed that the release of the drug from the vesicles inside the gel bases occurs in two stages. First, the drug is released from the vesicles that act as the drug reservoir and then diffuse through the gel network. The presence of a gel network makes it difficult to diffuse and thus slows down the release of the drug [20].

6.1 How to prepare niosomal gels?

The very low viscosity of the niosome is not suitable for topical use. Viscosity can be increased by adding thickening agents, changing the system's appearance, and thus affects drug release [21]. In order to make the niosomal suspension rheologically acceptable for topical applications, it is placed inside a carbopol hydrogel [22]. The hydrophilicity of carbopol and its adhesive properties make the gel containing niosome an effective carrier to increase the contact time at the target site [23]. Moreover, it can increase the time the drug remains at the absorption site by interacting with the skin mucosa [24]. Thickening agents in preparing gels containing niosome include carbopol 934, carbopol U21, carbopol 974 NF, carbopol 937, carbopol 980, carbopol 940, xanthan gum, poloxamer 407, and hydroxypropylmethylcellulose [21], [25]–[30].

The gelling agent is dispersed in distilled water or PBS (pH = 7.4) and kept in the dark for 24 hours until completely swollen. Drug-containing niosomes are then slowly added to the gel by continuous magnetic stirring [21], [25]. Continuous stirring can be done using a glass rod [31]. In order to avoid any risk of irritation when applied to the skin, the pH should be within the body's pH range [32]. Therefore, substances such as triethanolamine and sodium hydroxide are added to neutralize the pH of the gel [32], [33]. For example, in a recent study, sodium hydroxide (alkaline) was added to neutralize carbopol, which is acidic, to obtain a topical gel with the proper viscosity and pH for the skin [34]. Mixing is continued until a clear gel is formed [21].

In another study, the polymer was dissolved in PBS for gel formation by continuous magnetic stirring (pH = 7.4). The drug-loaded niosomes were then added and gently mixed until a homogeneous dispersion was formed. The gel was dispersed in the cooled solution, and the mixture was stored at 4 ± 2 ◦C for approximately 24 hours [25].

In another article, Polaxamer 407 gel was prepared using the cold method, the weighted amount of polymer was slowly added to the water with gentle mixing. The mixture was refrigerated overnight (4 ° C). After forming a clear, viscous gel, the selected niosomal dispersion was added to the cold solution and mixed gently with a glass rod. The solution was left at room temperature until a clear gel formed [35]. Refrigeration overnight can be essential for gel dispersion [36].

In another paper for each formulation, properly weighted amounts of alpha-lecithin from soy, cholesterol, surfactant, and drug were mixed with ethyl alcohol (95%) in a sealed glass vial. The glass vial was placed in a water bath for 30 minutes at 70-80 ° C with intermittent shaking until the liquids were wholly dissolved. The preheated phosphate-buffer saline (PBS) was then added to the melt liquid mixture and placed in a water bath for 10 minutes until the mixture became a clear solution. The mixture was allowed to cool at room temperature for 24 hours, and a gel containing creamy white proniosomes formed [37].

Finally, the gels can be placed in flexible and foldable aluminum tubes, sealed with a minimum of air, and then autoclaved [38].

7. CHARACTERIZATION OF GELS

The following tests are performed to ensure the suitability and safety of niosome-containing gels.

7.1 Ph

The pH of the gel should be compatible with the pH of the skin. In articles, the pH of the prepared gel is determined using a digital pH meter [21], [32]. For example, in one article, some gel containing niosome was mixed with distilled water by a homogenizer. The electrode was then immersed in the prepared gel solution, and the results were recorded using a digital pH meter [35].

7.2 Viscosity

In one study, the viscosity of the gel containing the niosome was measured using a stress control rheometer (connected to a thermostatic water bath for adjustment at 25 ° C). The gel containing the niosome

was placed on the viscometer plate, the viscosity was calculated using essential rheological software, and an average of 3 tests was used to determine the viscosity at room temperature [32], [39].

7.3 Fixed shear deformation

In a study investigating rheological behavior, the velocity gradually increased at a constant rate for all specimens tested until the torque reached 90% and was held for 30 seconds between two consecutive velocities. Viscosity, shear rate, and shear stress were obtained directly from the monitor after the velocity gradually decreased and reached the starting speed. All measurements were performed three times. Complete rheogram were obtained by plotting the shear rate relative to the shear stress and plotting the viscosity ratio relative to the shear rate. To investigate the rheological behavior, n (Farrow constant) was calculated using Equation (۱):

$$\log G=(n\times \log F) - \log \eta \qquad (۱)$$

Wherein

G = shear rate

F = shear stress

η = Non-Newtonian viscosity.

When n> 1, a pseudoplastic flow or shear thinning, and when n <1, a dilatant or shear-thickening flow were seen. It is understood that the gel should exhibit a pseudoplastic flow or shear thinning (a shear-thinning system shows a decrease in viscosity when shear stress is applied), which can be due to the immediate arrangement of the colloidal lattice structure, which can flow more easily in the cutting path within the layers [31], [33], [39].

7.4 Scalability

Scalability is a rheological property that determines the ease of topical application and affects drug delivery to the target site [33]. The expandability of the formulation is inversely affected by viscosity [21]. The study of the expandability of the gel containing niosomes is analyzed with a wooden block and a sliding glass device. The gel containing the niosome is placed on the bottom of the block, and the movable top plate is placed on the gel, and the time of complete separation of the top plate from the set is observed. Equation (۲) determines scalability:

$$s=(m\times l) \div t \qquad (2)$$

Wherein

S = scalability

m = weight held by the top plate

l = Length traveled by the top page

t = Time spent separating the page

In one study, the expandability of gel formulations containing niosomes was measured by placing some of the gel on a glass plate with a second glass plate on it. An increase in diameter was observed due to the dispersion of gels [26].

7.5 Physical assessment

The niosomal gel formulation, visually, for physical appearance, color, odor, homogeneity, clarity, presence of particles, phase separation or bleeding, as well as feeling when used (firmness, sand, and fat) when applied to the skin and also a few minutes after Uses are examined [25], [32], [35], [40].

7.6 Investigation of niosomal gel in vitro condition

7.6.1 Skin penetration and skin deposition studies

In one study, the rate of skin penetration and deposition on the skin of Wistar rats was investigated using a vertical Franz cell. The epidermal layer of the mouse skin was carefully removed and fixed to the donor chamber. Phosphate buffer penetration medium (pH = 7.4) was placed inside the penetration cell. The gels were applied to the donor chamber. The temperature was kept at 37 ° C. Samples were taken at various time intervals and replaced with a fresh medium to maintain the condition of the sink (existing conditions). Drug concentrations were determined using high-performance liquid chromatography (HPLC). At the end of penetration studies, the skin was removed and washed with distilled water. It was cut into small pieces and homogenized with methanol for complete drug extraction. HPLC examined the sample after proper dilution [33].

7.6.2 In vitro release studies

In one study, release studies were performed using a dialysis bag. Samples were taken at different time intervals using a visible spectrophotometer at 237 nm, and the percentage of drug released was determined [41].

8. RESULTS

The addition of niosomes to the gel base showed a satisfactory improvement in viscosity profile compared to the gel without niosomes. Cholesterol particles of niosomes form a colloidal network that places itself in the applied cutting path and thus improves viscosity compared to gels without niosomes; that is, it shows pseudoplastic behavior that facilitates its topical application. In addition, the viscosity of topical gels is inversely proportional to the degree of penetration. In general, increasing the system's viscosity can be the basis for a firmer structure and reduce drug release and penetration [32], [33].

The viscosity of carbopol gel has been reported to decrease with increasing temperature. High temperatures can cause the polymer structure of carbopol to disintegrate [30].

A gel containing niosomes showed a satisfactory improvement in scalability compared to a gel without the niosome. The results showed that the gel containing niosomes could be easily expanded by applying a small amount of incision; this may be due to the unique matrix structure of the gel containing niosomes due to the presence of cholesterol vesicles [32]. As the polymer concentration increased, the scalability decreased due to the increase in the viscosity of the formulation [42].

In vitro skin penetration was higher for niosome-containing gels than gels without niosome containing the same amount of drug after 24 hours; this is probably due to the presence of surfactant in the gel containing the niosome. Improving penetration by a surfactant is a well-known effect.

Another possible reason for more skin retention of niosome-containing gels may be that it provides a large surface area for drug delivery to the skin due to the small size of niosomes compared to niosomes-free gels [21].

A gel containing the niosomal drug showed more deposition inside the skin than without a niosomal drug. Better drug penetration and deposition can be justified by several mechanisms—nonionic surfactants in the formulation act as penetration enhancers. Surfactants in the vesicular form reduce the crystallinity of the intracellular lipid bilayer structure of the skin, thereby increasing drug deposition. The higher solubility of the drug increases its penetration through the skin [33].

Encapsulation of the drug in the niosomal gel system improves the transdermal penetration of the drug, controls the release of the drug, and prevents its destruction by protecting the drug from direct contact with the environment [21].

In an article, the release rate gradually decreased; this may be due to the slower diffusion rate due to the higher density of the gel. Delayed-release time can be due to the following two-stage events: First, proteins are released from the nanosystems, and then drug release occurs through the hydrogel. This result shows the effect of a significant percentage of gel formation on drug release [43].

It is clear that if niosomes are added to the structured gel, drug release is significantly slower ($p < 0.05$) compared to niosomal suspensions, this is probably due to the diffusion limit imposed by the gel polymer network (which provides an additional barrier to drug release from the niosomal vesicles) [35].

9. CONCLUSION

Finally, we can conclude that gels are a suitable substrate for niosomes, and gels containing niosomes are much more effective than gels without niosomes; therefore, it is predicted that in the future, the use of gels containing niosome for different applications will increase.

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