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DEVELOPMENT OF HERBAL DRUG -LOADED TOPICAL NIOSOMAL GEL FOR TREATMENT OF ECZEMA

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Abstract:

Skin conditions like eczema are frequently treated using a variety of medicinal plants. In many parts of the world, traditional herbal treatment is used extensively. Most people believe that herbal therapies work well and rarely have adverse effects. There is currently a lack of controlled clinical trials in humans for herbal medications. Clinical study on herbs hopefully opens up new treatment options. The term "eczema" refers to a group of medical diseases that irritate or inflame the skin. Due to numerous issues with the traditional treatment of steroidal molecules, a transdermal drug delivery system for steroidal drug molecules through the development of a niosomal gel is required for an improved drug delivery system. The aim and objective of the study was to develop herbal drug loaded niosomes as topical gel by using thin film hydration technique using Span series 20, 60, 80 and cholesterol has been successfully revealed. Niosomes addressed the problems of drug insolubility, instability, low bioavailability, and rapid degradation. This study provides an overview of niosomes preparation techniques and their uses in the pharmaceutical industry.

Keywords: Eczema**,** Herbal Extract, Niosomal Gel, Thin Film Hydration Technique.

INTRODUCTION

Eczema, also known as atopic dermatitis, is the most common form of dermatitis. In addition to genetic factors, environmental factors are believed to play an important role in pathogenesis. Eczema is most commonly seen in children, but can also be seen in adults. People with this condition tend to have dry, itchy skin that is prone to infection. Eczema is commonly known as an "itchy rash" because of dry skin that develops as a rash when scratched or rubbed. The most important treatment for eczema is to moisturize the skin, followed by topical steroids for redness. Eczema is a disease characterized by severe itching, swelling, lichenification and peeling. Both endogenous and exogenous factors can trigger this inflammatory response. Many herbs are used by locals to treat eczema.[1]

Figure 1: Eczema Disease Image

Etiology

Eczema patients have a malfunctioning barrier that contributes to a number of issues. For healthy skin hydration, the cells that make up our skin are crucial. Dry skin is a common symptom of eczema due to the breakdown of the skin barrier. Dehydrated skin results from the skin's increased ability to lose water. Additionally, those who have eczema are more prone to illness. The malfunction allows harmful chemicals to more easily infiltrate the skin. Atopic dermatitis patients frequently have an abnormally inflammatory immune response, and their skin is sensitive to allergens and odours.

Epidemiology

The lifetime prevalence of atopic dermatitis is approximately 15-30% in children and 2-10% in adults. About 60% of cases occur during the first year of life. The prevalence of atopic dermatitis is more common in rural areas than in cities. This prevalence highlights the link between lifestyle and environmental factors in the mechanism of AD. Atopic dermatitis is part of a third phase known as the "atopic march". It refers to the association between patients with atopic dermatitis, asthma, and allergic rhinitis. About 50% of patients with severe atopic dermatitis develop asthma and 75% develop allergic rhinitis**.** [2]

Pathophysiology

Research has shown that atopic dermatitis has a genetic component. One common mutation has been observed in the filaggrin gene, a gene essential for skin cell maturation. This gene is responsible for making the hard, flat keratinocytes that form the skin's outer protective layer. In patients with normal skin cells, keratinocytes are histologically dense. Patients with filaggrin mutations have a dysfunctional skin barrier due to the disordered organization of skin cells.[3]

Patients with eczema have a broken barrier, which causes a variety of problems. The cells that make up our skin are essential for optimal skin hydration. A typical sign of eczema is dry skin because the skin barrier has been compromised. Skin that is dehydrated has a greater capacity to lose water. Eczema sufferers are also more vulnerable to sickness. The flaw makes it easier for dangerous chemicals to penetrate the skin. Patients with atopic dermatitis usually experience an abnormally inflamed immune response, and their skin is also highly sensitive to allergens and odours.[4]

Management And Treatment

Primary management and treatment of atopic dermatitis include hydration and topical anti-inflammatory drugs for flare-ups. The priority for treatment is daily skin hydration therapy using unscented ointments with limited preservatives.[5] Ointments are preferable to creams because lotions have a high water-to-oil ratio. Patients/parents should identify and address triggers. Advice should be given to avoid environmental allergens, harsh soaps and detergents, fragrances, and harsh or non-breathable fabrics. Skin flare-ups can be treated with topical anti-inflammatory drugs, such as topical steroids, or non-steroidal products such as pimecrolimus, tacrolimus, and euthyrsa. In children, itching is worse at night. Oral antihistamines can be used intermittently at bedtime for itchy sleep disturbances. However, antihistamines are no longer recommended for daytime uses for itching in eczema. Patients with poorly controlled atopic dermatitis are at increased risk of skin infections. Patients/parents may be instructed to use diluted bleach baths or intranasal mupirocin to reduce the number of skin infections.[6]

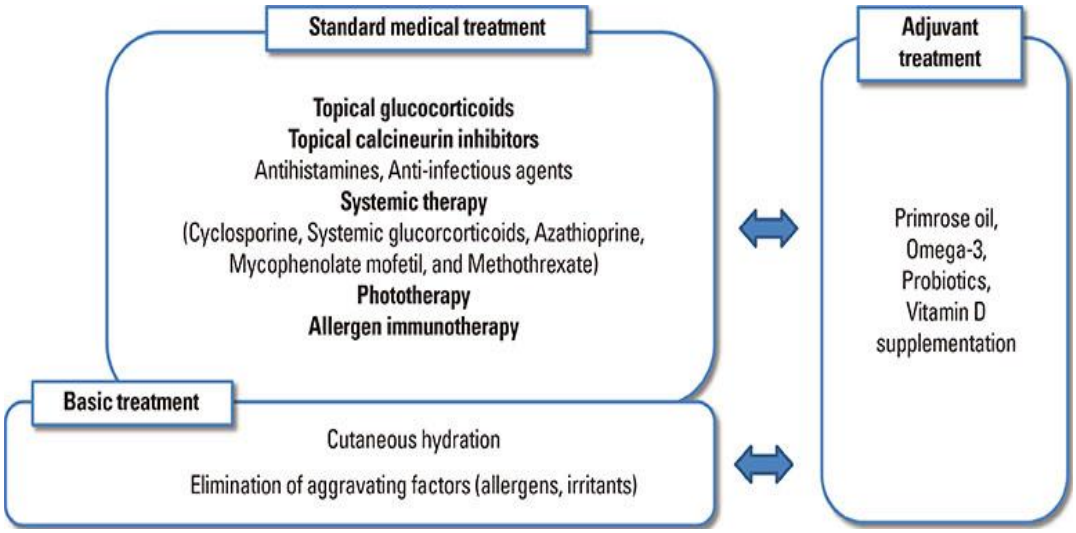

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Figure 2: Treatment of Eczema

Differential Diagnosis [7]

The differential diagnosis for atopic dermatitis includes may eczematous dermatitis including:

- Contact dermatitis
- Cutaneous fungal infections
- Seborrheic dermatitis
- Drug eruptions
- Scabies
- Psoriasis
- Ectodermal dysplasia
- Hyper IgE syndrome
- Netherton's syndrome
- Wiskott-Aldrich syndrome

HERBAL FORMULATION

An herbal preparation is one or more herbs or herbs used to diagnose, treat, alleviate, alter the structure or physiology of, or provide a specific nutritional benefit to an animal in humans or animals. Means a dosage form that contains a specific number of processed herbs. An herbal preparation contains an active ingredient or herbal substance, or an herbal preparation or herbal substance in combination with one or more herbal preparations. Herbal preparations are obtained by subjecting herbal substances to processes such as extraction, distillation, pressing, fractionation, purification, concentration, fermentation, and grinding or powdering. Whole plants, fragmented or cut plants, plant parts, algae, fungi, lichens in untreated, mostly dried, but sometimes fresh form, were used to make herbal preparations. Plant matter is precisely defined by the part of the plant used and the botanical name according to the binomial system (genus, species, variety, and author). Various herbal preparations include tinctures, extracts, essential oils, juices, and processed exudates. A marker is a chemically defined component or group of components of an herbalsubstance, formulation, or pharmaceutical of interest for control purposes, whether therapeutic or not. If the marker in the plant or plant preparation has been quantified, the marker is used to calculate the amount of plant or plant preparation in the plant preparation. Characterization of herbal formulations including design and development, pharmacopoeia testing and acceptance criteria, routine testing, release, shelflife acceptance criteria, in-process testing, alternative processes, evolving techniques, reference standards, and statistical concepts. Herbal medicine has been used for as long as there has been humankind, and throughout the past century, numerous plant extracts have been the subject of chemical and pharmacological studies to determine their chemical makeup and corroborate the traditional medical indications. About 500 distinct plant species are utilised as essential ingredients in phytomedicine, which has experienced a recent surge in popularity. Many of these species are still being harvested from the wild. There is a growing acceptance of supplementary or alternative medicine, and herbal medicines are experiencing a similar increase in popularity.

Aloe vera (A. Barbadensis) (Family Liliaceace) entire leaves are known to support cellular repair, digestion, and the assimilation of meals, vitamins, minerals, and other essential components to revitalise the skin. The use of the fresh gel, juice, or manufactured products has been made to improve general health as well as for cosmetic and medical objectives. There have been herbal medicines for thousands of years. It still has a significant following in Asia and has its roots in China and India. Researchers in the fields of ethnopharmacology, botany, microbiology, and natural product chemistry are scouring the planet for phytochemicals that may one day be used to treat infectious diseases. On Earth, there are between 250,000 and 500,000 different plant species. Although it differs greatly between nations, their therapeutic, pharmacological, and economic usefulness is nevertheless being recognised. Aloe vera (A. Barbadensis) (Family Liliaceace) entire leaves have been shown to promote cellular repair and healing. In recent years, both the demand for and use of medications and nutritional supplements derived from plants has increased. Due to their ability to treat human illnesses, plants are a major factor in the development of new therapeutic medicines. Higher plants have medicinal potential due to the existence of secondary metabolites, which includes antioxidant, antimutagenic, and anticarcinogenic qualities. [8, 9, 10]

Herbal medicine is the most popular form of traditional medicine with a long history. Information is passed on from generation to generation. Different herbs have different therapeutic responses. Jujube extract, for example, is used orally by the general public to treat eczema. It was effective 90% of the time, but not 10%. The same treatment was very effective for some people and completely ineffective for others. The WHO reports that more than 80% of people in Asia rely on traditional medicines to treat their ailments. I rely on you. Such drugs are used to treat various chronic diseases, such as skin diseases and various infections. The term "traditional medicine" refers to the theories, beliefs, and personal It is the sum of experience-based knowledge, skills, and practices, mental health. Large segments of the population in developed as well as developing countries rely on herbal remedies.[11]

Plants Famous for Their Efficacy in Eczema

Jujube

The most widely farmed plant in the world is Ziziphus jujuba (jujube), also known as the red date or Chinese date. It is a little deciduous tree with broad, glossy green leaves, tiny blooms, and edible fruit. Fruit looks like an apple when it is young and shrinks to the size of a date as it ages. 15 A fruit snack is common. It has long been used medicinally to treat stress. 16 Additionally, it has activity against germs, fungi, inflammation, 17 antioxidants, and wounds. 18 In the arid region of Cholistan, jujube extract is consumed before breakfast. Although there is no scientific research on it for eczema, the indigenous people utilise it as a treatment. Use over time enhances complexion. [12,13,14]

Walnut

Juglans regia is a tall, 25–35 m long deciduous plant that thrives in dense forest competition. It is a light-loving plant that needs direct sunlight to thrive. Large, alternately placed leaves with noticeable veins. Walnut leaves and their tannins interact with skin cells in a way that makes them resistant to allergies and microbial-based illnesses. Although walnut extract also exhibits excellent antioxidant activity, there are no clinical investigations on its application.

Chamomile

The chamomile plant, Matricaria recutita, resembles a daisy (Figure 3). It is well known for its tea, which is sometimes served with honey or lemon and used to treat sleep issues. It is traditionally believed to be useful in treating cancer, sleep difficulties, cancer, and gastrointestinal issues like gas and diarrhoea. It is utilised in allergic diseases, atopic dermatitis, and eczema because it is efficient in healing wounds and inflammatory skin problems. Tea, extracts in liquid form, capsules, and tablets all contain flowers. It is administered to the skin as a cream or ointment. conducted scientific research on 161 people with eczema using chamomile extract cream. It was similarly effective when compared to steroidal and nonsteroidal creams. [15,16]

Calendula

As it faces the sun, the annual herbaceous plant Calendula officinalis resembles a daisy and is often called a marigold (Figure 4). [17] It has historically been used as an anti-inflammatory and for the treatment of eczema, acne, and cramps. It is used to treat stomach cramps and constipation because the hydroalcoholic extract it produced in rabbit jejunum had spasmolytic and spasmogenic effects. [18] Its anticancer efficacy was demonstrated in a second mouse trial. Its extract also demonstrated anti-inflammatory and antiviral properties. It is efficient for treating radiation damage, dermatitis, acne, inflammation, and bleeding when applied topically as a cream or ointment. [19]

Liquorice

The herbaceous perennial legume Glycerrhiza glabra has long blooms and pinnately divided leaves. Coughs are historically treated using its root. It is said to have laxative, antiviral, anti-ulcer, and hepatoprotective properties. It aids in the recovery of stomach and duodenal ulcers by preventing the growth of Helicobactor pylori. In a double-blind, placebo-controlled trial, 30 eczema patients evaluated the efficacy and safety of G. glabra. Different licorice extract gel formulation doses were applied for two weeks, and clinical parameters like erythema, itching, scaling, and edoema were graded on a four-point scale: absent=0, mild=1, moderate=2, severe=3. After one and two weeks, it was found that licorice extract 1% and 2% gel produced greater results than a placebo in terms of reducing erythema, irritation, and edoema. Gel made from licorice extract, however, had no effect on the scaling. At the end of two weeks, 2% of the two formulations had improved outcomes. Patients reported no negative effects. [20,21,]

Aloe vera

In Pakistan, aloe vera is referred to as quargandal. The plant can be found in regions with arid climates (Figure 5). A. vera is a succulent plant without stems that can reach heights of 60 to 100 cm. The broad, emerald-green leaves bear teeth-like horns and serrated edges. Summertime brings about pendulous flowers with 2-3 cm long yellow tubular corollas. Traditionally, A. vera is used to treat a variety of illnesses. It is applied externally to soothe irritated skin and

aid in the healing of wounds. [22] Internally, it is used as a dessert [23] to treat conditions including psoriasis, diabetes mellitus, hyperlipidemia, hepatitis, heartburn, indigestion, [24] and liver diseases like hepatitis. [28] Antibacterial and antifungal activities can be found in A. vera extracts. When treating eczema, its gel (Figure 5) is immediately administered to the affected areas. Antibacterial and antifungal activities can be found in A. vera extracts. Its gel (Figure 5) is immediately administered to the body regions with eczema. Its hydrating effects make the skin smoother and hasten the healing of wounds. Many people claim that their eczema symptoms, such as skin dryness and scaling, have decreased. Because of its antibacterial qualities, it also helps to prevent secondary infection. A. vera cream was compared to a placebo in a randomised, double-blind clinical trial with 60 patients who had mild to moderate persistent psoriasis. With A. vera cream, the cure rate was 83% compared to 7% with placebo. [29]

Figure 3 :Chamomile flower

Figure 4:Calendula flower

Figure 5: *Aloe vera* plant and gel.

NIOSOMES

The microscopic lamellar structures known as niosomes or non-ionic surfactant vesicles are created when non-ionic surfactant of the alkyl or dialkyl polyglycerol ether and cholesterol are combined, followed by hydration in aqueous solutions.[30] The non-ionic surfactant span-60, which forms vesicles in niosomes, is often stabilised by the addition of cholesterol and a tiny quantity of an anionic surfactant like dicetyl phosphate. [31]

Niosomes, a vesicular form of non-phospholipids that can replace liposomes, were initially reported by. Niosomes are tiny, lamellar structures that are created when cholesterol and a single, non-ionic alkyl chain are mixed together and then hydrated in water. Niosomes have the ability to entrap both hydrophilic and hydrophobic pharmaceuticals when used as drug carriers. The microscopic lamellar structures known as niosomes or non-ionic surfactant vesicles are created when non-ionic surfactant of the alkyl or dialkyl polyglycerol ether and cholesterol are combined, followed by hydration in aqueous solutions [30]. A non-ionic surfactant like span-60, which is typically stabilised by the addition of cholesterol and a little quantity of a, is the amphiphile that forms vesicles in niosomes. in contrast to phospholipids Synthetic non-ionic surfactants used to make niosomes are chemically stable, precise in their chemical makeup, and less expensive than those used to make liposomes. Niosomes are said to achieve and maintain more stability than liposomes and to be able to prolong the circulation of the drugs they have contained. They have better intrinsic targeting potential and tendency towards the liver, brain, and tumour due to the presence of non-ionic surfactant. Microscopic lamellar structures called niosomes or non-ionic surfactant vesicles are generated. It might be highly helpful for better treatment targeting against microbial diseases including cancer, parasitic viruses, and others. The most popular routes of administration, including intravenous, intramuscular, subcutaneous, ophthalmic, oral, and

transdermal, have been studied for drug delivery using niosomes. Niosomes have been thoroughly investigated in recent years for their potential to function as delivery systems for medicines, antigens, hormones, and other bioactive substances. The targeting of the bioactive chemical to the sick tissue and the slow release that results from its encapsulation within niosomes prevents early biodegradation or inactivation, changes its distribution, metabolic stability, and toxic symptoms.[32]

Salient features of niosomes

- Niosomes can entrap solutes.
- Niosomes are osmotically active and stable.
- Niosomes have an infra-structure comprising of hydrophobic and hydrophilic for the most part together thus likewise oblige the medication atoms with an extensive variety of dissolvability.
- Niosome discharge the medication in a controlled way by means of its bilayer which give supported arrival of the encased medication, so niosomes fill in as medication warehouse in the body.
- Targeted medication conveyance can likewise be accomplished utilizing niosomes the medication is conveyed specifically to the body part where the remedial impact is required. There by lessening the measurement required to be managed to accomplish the coveted impact.
- They improve the solubility and oral bioavailability of poorly soluble drugs and also enhance the skin permeability of drugs when applied topically.
- Niosomes exhibits flexibility in their structural characteristics (composition, fluidity and size) and can be designed according to the desired situation.
- Niosomes can improve the performance of the drug molecules.
- Better availability to the particular site, just by protecting the drug from biological environment.
- Niosomes increase the stability of the entrapped drug. **[33,34]**

ADVANTAGES:

1. Niosomes increase the bioavailability of drug by shielding/ protect the drug from acidic and enzymatic degradation in GIT due to this it increases/ improves the bioavailability of drug.
2. Niosomes structure are hydrophilic, lipophilic and amphiphilic in nature due this we incorporate variety of drug moieties and used for many drugs.
3. Niosomes are osmotically active and stable in nature.
4. Skin permeation is also be increased by the use of niosomes.
5. The therapeutic efficiency of drug molecules is improved by slow down the clearance from the circulation.
6. Surfactant can be handled and store easily with no specific condition.
7. The vesicles behave as a depot and drug can be release in controlled manner.
8. Patience compliance is higher in oily dosage from. [35,36]

DISADVANTAGES:

1. Aggregation of drug molecules.
2. Physical instability.
3. Entrapped drug can leak.
4. Hydrolysis can decrease the shelf life of encapsulated drug.
5. Time consuming. [37]

MECHANISM OF NIOSOMES FORMATION

Non-ionic amphiphiles self-assemble into closed bilayer structures in aqueous conditions to produce non-ionic surfactant-based vesicles. Rarely does the assembly into closed bilayers occur spontaneously; instead, energy inputs like heat or physical agitation are typically involved. The end result is an assembly where the hydrophilic head groups have the most contact with the aqueous solvent while the hydrophobic portions of the molecule are protected from it. [38,39]

- **Types of Niosomes [40]**

Bola surfactant containing niosomes

The usage of surfactants in Omega hexadecylbis-(1-aza-18 crown-6) (bola surfactant): span-80/cholesterol in a 2:3:1 molar ratio makes up bola surfactant-containing niosomes.

Proniosomes

Proniosomes are created from a mixture of carriers and surfactants. Proniosomes are hydrated, and then niosomes are created.

Aspasomes

Acorbyl palmitate, cholesterol, and an extremely charged lipid called diacetyl phosphate are combined to create aspasomes, which cause vesicles to form. Aspasomes are first hydrated with a water or fluid solution before being sonicated to extract the niosomes. To increase the transdermal saturation of medicines, aspasomes can be used. Aspasomes have a natural cell-reinforcing property, they have also been used to reduce scatter brought on by reactive oxygen species.

Niosomes in Carbopol gel

Niosomes were made from drugs, spans, and cholesterol and then added to a carbopol-934 gel base made out of propylene glycol (10% w/w), glycerol (30% w/w), and water (1% w/w).

Vesicles in water and oil system (v/w/o)

The aqueous niosomes are incorporated into an oil stage frame vesicle in a water in oil emulsion (v/w/o) in this technique. Niosome solution made of sorbitol monostearate, cholesterol, and solulan C24 (Poly-24-Oxyethylene cholesteryl ether) can be expanded to oil stage at 60 0C to achieve this. This causes a vesicle in water in oil (v/w/o) emulsion to form, and when it cools to room temperature, it transforms into a vesicle in water in oil gel (v/w/o gel). After oral administration and controlled release, the v/w/o gel can entrap proteins and proteinous medicines while also shielding it from enzymatic breakdown.

Niosomes of hydroxyl propyl methyl cellulose

In this form, niosomes were initially added to a base that already included 10% glycerin of hydroxypropyl methyl cellulose.

Deformable niosomes

The mixture of non-ionic surfactants, ethanol and water forms the deformable niosomes. These are smaller vesicles and easily pass through the pores of stratum corneum, which leads to increase penetration efficiency. It can be used in topical preparation [41,42]

The niosomes are also classified according to the number and size of bilayer which is as follows,

i) Multi Lamellar Vesicles (MLV): Multilamellar vesicles are the most widely used niosomes. It consists of a number of bilayers. The approximate size of vesicles is 0.5-10 μm diameter. It is simple to make and are mechanically stable upon storage for long periods.

ii) Large Unilamellar Vesicles (LUV): These are the large unilamellar vesicles which having a high aqueous/lipid compartment ratio, so that larger volumes of bio-active materials can be entrapped.

iii) Small Unilamellar Vesicles (SUV): These small unilamellar vesicles are mostly prepared from multilamellar vesicles by sonication method, French press and extrusion method.

STRUCTURE OF NIOSOME

A typical niosomes vesicle would consist of a vesicle Forming amphiphilic i.e., a non-ionic surfactant such As Span-60, which is usually stabilized by the addition of cholesterol and a small amount of anionic Surfactant such as diacetyl phosphate, which also Helps in stabilizing the vesicle.

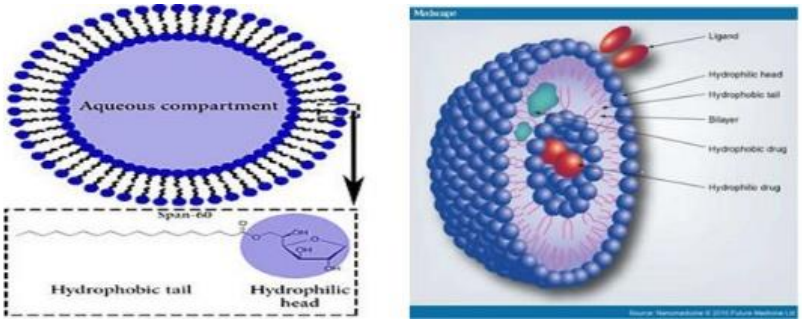

Figure No 6: Structure of Niosomes

COMPOSITIONS OF NIOSOMES:

The two major components used for the preparation of niosomes are,
1. Cholesterol

2. Nonionic surfactants

Cholesterol: Cholesterol is a steroid derivative, which is used to Provide rigidity and proper shape, conformation to the niosomes preparations.
Nonionic surfactants: The nonionic surfactants possess a hydrophilic head and a hydrophobic tail. The following non-ionic surfactants are generally used for the preparation of niosomes. e.g.

- Spans (span 60, 40, 20, 85, 80)
- Tweens (tween 20, 40, 60, 80)
- Brij's (brij 30, 35, 52, 58, 72, 76) [43]

Drugs used in Niosomal delivery [44]

Sr. No	Route Of Administration	Examples Of Drug
1.	Inhalation	All trans retinoic acids
2.	Intravenous route	Doxorubicin, comptothecin, zidovudine,insulin,cisplatin, rifampicin
3.	Nasal route	Sumatriptan
4.	Ocular route	Timolol maleate, cyclopentol
5.	Transdermal route	Piroxicam,estradiol, nimesulide

PREPARATION METHODS OF NIOSOMES [45]

1. Ether injection method
2. Hand shaking method
3. Sonication
4. Micro fluidization
5. Multiple membrane extrusion method
6. Reverse phase evaporation method (REV)
7. Trans membrane pH gradient Uptake process
8. The "Bubble" method
9. Formation of Niosomes from Proniosomes
10. Passive trapping technique
11. Ethanol injection method
12. Down sizing

13. Miscellaneous methods:
    a) Emulsion method
    b) Heating method

Ether injection method

Essentially, the ether injection method involves gradually infusing a surfactant solution dissolved in diethyl ether into warm water kept at 60°C. Through a 14-gauge needle, the surfactant combination in ether is injected into the material's aqueous solution. Ether vapourization results in the creation of vesicles with only one layer. The parameters employed and the particle size of the niosomes generated range from 50 to 1000 nm in diameter. Thin film hydration process by hand shaking. In this procedure, the surfactant and cholesterol are dissolved in a round-bottomed flask with a volatile organic solvent (such as diethyl either, chloroform, or methanol). Using a rotary evaporator, the organic solvent is evaporated at room temperature (20°C), leaving a thin coating of solid mixture deposited on the flask wall. Multilamellar niosomes can be produced by rehydrating the dried surfactant film with aqueous phase at 0 to 60 °C while gently stirring. [46,47]

Hand shaking method

In this procedure, a mixture of surfactant and cholesterol (150 micromoles) was dissolved in 10 millilitres of diethylether in RBF. At ambient temperature, the ether is rotational evaporated while under vacuum. The surfactant swells and forms a film that is pulled off the support when it becomes hydrated. Vesicles are finally formed when swollen amphiphiles fold. The volume of liquid trapped inside vesicles seems to be only 5–10%.

Sonication

The sonication approach was used by Baillie et al. in 1986 to create niosomes. In this procedure, a mixture of surfactant and cholesterol (150 micromoles) was dissolved in 2 ml of aqueous phase in a vial. For three minutes at 600 C, the dispersion is subjected to probe sonication. This technique entailed creating MLVs that vibrate at ultrasonic frequencies. Sonicators come in two varieties: Probe and Bath. When the sample volume is small, a probe sonicator is used, and when the sample volume is large, a bath sonicator is used.[48]

Micro fluidization method

A more recent method for creating unilamellar vesicles with a specific size distribution is micro fluidization. This technique is based on the submerged jet principle, in which two fluidized streams contact in precisely planned microchannels inside an interaction chamber at extremely high speeds. The arrangement of the thin liquid sheet impingement along a single front ensures that the energy supplied to the system stays in the region where niosomes form. The generated niosomes are more homogenous, smaller, and more reproducible as a result.[49]

Reverse Phase Evaporation Technique (REV)

In this procedure, a solution of ether and chloroform is used to dissolve the surfactant and cholesterol (1:1). This is combined with an aqueous phase that contains a medication, and the combined two phases are then sonicated at 4-5°C. After adding phosphate buffered saline, a transparent gel forms and is further sonicated (PBS). Low pressure is used to remove the organic phase at 40 °C. In order to produce niosomes, the resulting viscous noisome suspension is diluted with PBS and heated on a water bath at 60°C for 10 min. pH gradient in trans membranes (inside acidic) Process for Taking Drugs, or Remote Loading Method Chloroform is used to dissolve a surfactant and cholesterol solution. Next, a thin film is formed on the wall of the flask with a round bottom as the solvent evaporates under reduced pressure. This film is hydrated with 300mm citric acid (PH 4.00) by vertex mixing. The resulting multilamellar vesicles are then shared, frozen, and sonicated three times. To this niosomal suspension, aqueous solution containing 10 mg/ml of drug is added and vortexes. The PH of the sample is then raised to 7.0-7.2 with 1M disodium phosphate. Niosomes are produced by heating this mixture for 10 minutes at 60 °C. [50]

The Bubble Method

The bubbling unit is a three-necked flask with a spherical bottom that is placed in a water bath to regulate temperature. Nitrogen is supplied through the third neck, and the first and second necks include a water-cooled reflux and thermometer. In this buffer (PH 7.4), cholesterol and surfactant are dispersed simultaneously. The dispersion is then blended for 15 seconds with a high shear homogenizer before being instantly "bubbled" at the same temperature with nitrogen gas to produce niosomes. [51]

FACTORS AFFECTING PHYSICO-CHEMICAL PROPERTIES OF NIOSOMES

Various factors that affect the physico-chemical properties of niosomes are discussed further.

Amount and type of surfactant

The mean size of niosomes increases proportionally with increase in the HLB of surfactants like Span 85 (HLB 1.8) to Span 20 (HLB 8.6) because the surface free energy decreases with an increase in hydrophobicity of surfactant. The bilayers of the vesicles are either in the supposed fluid state or in gel state, contingent upon the temperature, the kind of lipid or surfactant and the nearness of different segments, for example, cholesterol. In the gel state, alkyl chains are available in an all-around requested structure, and in the fluid express, the structure of the bilayers is more confused. The surfactants and lipids are portrayed by the gel-fluid stage change temperature (TC). Phase transition temperature (TC) of surfactant also effects entrapment efficiency i.e., Span 60 having higher TC, provides better entrapment.[52]

Nature of Surfactants

A surfactant utilized for readiness of niosomes must have a hydrophilic head and hydrophobic tail. The hydrophobic tail may comprise of maybe a couple alkyl or perfluoroalkyl gatherings or now and again a solitary steroidal gathering. The hydrophobic tail of ether sort surfactants with single chain alkyl is more poisonous than comparing dialkylether chain. The ester type surfactants are chemically less stable than ether type surfactants and the former is less toxic than the latter due to ester-linked surfactant degraded by esterase's to triglycerides and fatty acid. The surfactants with alkyl chain length from C12-C18 are suitable for preparation of niosomes. Surfactants such as C16EO5 (poly-oxyethylenecetyl ether) or C18EO5 (polyoxyethylenesteryl ether) are used for preparation of polyhedral vesicles. Span series surfactants having HLB number of between 4 and 8 can form vesicles. [52]

Nature of encapsulated drug

The physic synthetic properties of typified medicate impact charge and unbending nature of the niosome bilayer. The medication cooperates with surfactant head gatherings and builds up the charge that makes shared aversion between surfactant bilayers and subsequently expands vesicle estimate. The aggregation of vesicles is prevented due to the charge development on bilayer. In Polyoxyethylene Glycol (PEG) coated vesicles; some drug is entrapped in the long PEG chains, thus reducing the tendency to increase the size. The hydrophilic lipophilic balance of the drug affects degree of entrapment. [53]

Structure of surfactants

The geometry of vesicle to be shaped from surfactants is influenced by surfactant's structure, which can be characterized by basic pressing parameters. Geometry of vesicle to be shaped can be predicated on the premise of basic pressing parameters of surfactants. Critical packing parameters can be defined using following equation,

CPP (Critical Packing Parameters) =V/lc × a0

Were,

V = hydrophobic group volume,

lc = the critical hydrophobic group length,

a0= the area of hydrophilic head group

Critical packing parameter value type of miceller structure formed can be ascertained as given below, If CPP < ½ formation of spherical micelles,

If ½ < CPP < 1 formation of bilayer micelles,

If CPP > 1 formation inverted micelles. [54]

Temperature of hydration

Hydration temperature influences the shape and size of the niosome, temperature change of niosomal system affects assembly of surfactants into vesicles by which induces vesicle shape transformation. Ideally the hydration temperature for noisome formation should be above the gel to liquid phase transition temperature of system. [53]

Resistance to osmotic stress

Addition of a hypertonic salt solution to a suspension of niosomes brings about reduction in diameter. In hypotonic salt solution, there is initial slow release with slight swelling of vesicles probably due to inhibition of eluting fluid from vesicles, followed by faster release, which may be due to mechanical loosening of vesicles structure under osmotic stress. [55]

NIOSOMES AS DRUG CARRIER SYSTEM

- Retain drugs qualitatively
- Exhibit long plasma half-lives
- Have high entrapment efficiencies
- Retard drug metabolism
- In the case of site-directed drugs. Allow the attachment of targeting ligands to the vesicle surface and assist in the movement of drugs across membranes. [56]

CHARACTERIZATION OF NIOSOMES:

1. Vesicle diameter
2. Vesicle charge
3. Bilayer formation
4. Number of lamellae
5. Membrane rigidity and homogeneity
6. Encapsulation efficiency
7. Stability study
8. Separation of unentrapped drug
9. Optical microscopy
10. In vitro drug release

a) Dialysis Tubing,
b) Reverse dialysis and
c) Franz diffusion cell [57]

Bilayer Rigidity and Homogeneity:

The Biodistribution and biodegradation of niosomes are Influenced by rigidity of the bilayer. In homogeneity can Occur both within niosome structures and between Niosomes in dispersion and could be identified via. P-NMR, Differential scanning calorimetry (DSC) and Fourier transform-infra red spectroscopy (FT-IR) Techniques.

Size and Shape: Various methods is used for the Determination of mean diameter like as laser light Scattering method besides it also determines by electron Microscopy, molecular sieve chromatography, photon Correlation microscopy, optical microscopy.

Stability Study:

Niosomal formulations are subject to Stability studies by storing at 4°C, 25°C and 37°C in Thermostatic oven for the period of three months. After One month, drug content of all the formulations is Checked by entrapping efficiency parameter.

In-vitro Release: In-vitro release rate study carried Out by the use of

i.Dialysis Tubing,

ii.Reverse dialysis and

iii.Franz diffusion cell.

Dialysis Tubing:

A dialysis sac is washed withdistilled water. The prepared vesicle suspension is pipetted into a bag made up of the tubing dialysis and after that the bag is sealed. Then the bag containing the vesicles is placed in 200 ml of buffer solution in a 250 ml beaker with constant shaking at 25°c. At various time intervals, the buffer is an analysis of the drug content of an appropriate assay method.

Reverse Dialysis:
A number of small dialysis as Containing 1ml of dissolution medium is placed in Proniosomes. The proniosomes are then displaced into the dissolution medium. The direct dilution of the Proniosomes is possible with this method and the rapid Release cannot be quantified by using this method.

Franz Diffusion Cell:
The in vitro diffusion studies can be performed by using franz diffusion cell. Proniosomes is placed in the donor chamber of a franz diffusion cell fitted with cellophane membrane. The proniosomes is then dialyzed against a suitable dissolution medium at room temperature; the samples are withdrawn from the medium at suitable intervals and analyze for drug content using suitable method such as u.v spectroscopy, HPLC, etc. The maintenance of sink condition is essential.

Scanning Electron Microscopy:
The niosomes were observed under a scanning electron microscope (SEM) they were mounted directly onto the SEM sample stub using double sided sticking tape and coated with gold film of thickness of 200 nm under reduced pressure of 0.001 mmhg. Photographs were taken at suitable magnification.

Vesicle Charge:
The vesicle surface charge can play an important role in the behavior of niosomes in vivo and in vitro. Charged niosomes are more stable against aggregation and fusion then unchanged vesicles. In order to obtain an estimate of the surface potential, the zeta potential of individual niosomes can be measured by micro electrophoresis. An alternative approach is the use of PH-sensitive fluorophores. More recently, dynamic light scattering has been used to measure the zeta potential of niosomes.

Niosomal Drug Loading and Encapsulation Efficiency:
To determine drug loading and Encapsulation efficiency, the niosomal aqueous Suspension was ultra-centrifuged, supernatant was Removed and sediment was washed twice with distilled Water in order to remove the adsorb drug. The entrapment efficiency (EE) was then calculated Using formula:

$$\text{Percentage entrapment (\%E)} = \frac{\text{Entrapped drug (mg)}}{\text{Total drug added (mg)}} * 100.$$

The drug loading was calculated as: [58-63]

$$\text{Drug loading} = 1 + \frac{\text{Amount of drug in niosomes}}{\text{Amount of niosomes}*100}$$

APPLICATIONS OF NIOSOMES
Niosomal drug delivery for their action against various diseases is potentially applicable to many pharmacological agents. Few of its treatment applications are as follows:

Targeting of bioactive agents

1. The reticuloendothelial system, first (RES)
The vesicles prefer to reside in RES cells. Due to circulating serum components that designate them for clearance, they are known as opsonins. However, such localised medication accumulation has been used to treat parasite hepatic infection and animal cancers known to metastasis to the liver and spleen.[64]

2. To organs other than reticulo-endothelial system (RES)

By using antibodies, the carrier mechanism can be directed to particular locations within the body. Since immunoglobulins frequently have lipid surface attachment, they offer a practical way to target the drug carrier. The natural ability of many cells to identify and bind particular carbohydrate determinants can be utilised to route the carrier system to particular cells. [65,66]

Neoplasia

Doxorubicin, an anthracyclic antibiotic, exhibits broad-spectrum anti-tumor action as well as a dose-dependent, irreversible cardiotoxic impact. The drug's niosomal drug trapping lengthened its half-life, as well as the drug's circulation and metabolism. The lifespan of the mice was extended and the frequency of sarcoma growth was reduced when the S-180 tumor-carrying mice were given this medication by niosomal administration. [67] Niosomal methotrexate causes a complete tumour regression, greater plasma rates, and a slower clearance when given intravenously to mice with S-180 tumours. [68,69]

Delivery of peptide drugs

Niosomal trapped oral administration of 9-desglycinamide, 8 arginine vasopressin was investigated and found to dramatically increase peptide stability in an in-vitro intestinal loop model. [70]

Immunological applications of niosomes

Researchers have examined the fundamentals of the immune response triggered by antigens using niosomes. Niosomes have been recognised as a powerful adjuvant due to their immunological specificity, low toxicity, and stability. [71] The niosome as a vehicle for Hemoglobin Niosomal suspension can be utilised as a haemoglobin carrier since it has a visible spectrum that can be overlaid on free haemoglobin. Vesicles can modify the shape of the hemoglobin-dissociation curve just like non-encapsulated haemoglobin because they are oxygen-permeable as well. [72]

Transdermal deliveryof drugs by niosomes

Since slow drug absorption via the skin is the primary problem of transdermal drug delivery for other dosage forms, niosome-based transdermal drug delivery has improved in penetration rate. On hairless mice, various formulations of erythromycin have been explored for topical distribution, including niosomes. Confocal microscopy has revealed that non-ionic vesicles can be made to specifically target pilosebaceous glands. [73]

Carrier for haemoglobin

The importance of niosomes as haemoglobin carriers is significant. The niosomal haemoglobin suspension produces a super-imposable curve on the free haemoglobin curve. [74, 75]

Cosmetic delivery

In the 1970s and 1980s, L'Oreal created and patented niosomes, which were the basis for the first report of non-ionic surfactant vesicles for cosmetic applications. And Lancôme debuted its first product, called Noisome, in 1987. Niosomes are highly capable of increasing the bioavailability of substances that aren't easily absorbed, improving the stability of medications that are entrapped, and lastly enhancing skin penetration. This opens the door for niosomes in the field of cosmetic and skin care applications. [76].

Vaccine delivery

Niosomes receive good attention for topical vaccination and the peroral vaccine delivery system. Using the reverse phase evaporation approach with Span 85 and cholesterol, niosomes for topical DNA delivery of Hepatitis B surface antigen (HBsAg) were created. When the immune stimulating activity was examined, it was discovered that topical niosomes, as opposed to topical liposomes and intramuscular recombinant HBsAg, elicited equal amounts of endogenous cytokines and serum antibody titers. [77,78].

Other Applications

a) Sustained Release

Drugs having a low therapeutic index and a higher water solubility may be kept in the bloodstream through niosomal encapsulation, and niosomes can produce continuous release action. After the liver cells absorb the drug, it is suggested that the liver serve as a methotrexate depot. [79]

b) **Localized Drug Action**

Because of the size of niosomes and their poor capacity to penetrate connective tissue and epithelium, niosomal dosage form is one method for producing localised therapeutic activity. The medication is located at the site of administration. For example, mononuclear cells ingest antimonials encapsulated inside niosomes, resulting in product localization, improved potency, and consequently decreased in both dose and toxicity. This increases the drug's efficacy and potency and also reduces its systemic adverse effects. [80, 81]

FUTURE PROSPECTS

A potential medication delivery molecule is the niosome. There is a lot of room to include harmful anti-cancer, anti-infective, anti-aids, anti-inflammatory, antiviral, etc. medications. Utilizing niosomes as potential drug delivery systems will improve the bioavailability and targeting capabilities of the medications while lowering their toxicity and side effects. Niosomal carriers are safer than ionic drug carriers, which are more toxic and inappropriate. Noisy doesn't need to be handled or stored under any special circumstances.

CONCLUSION

A novel drug delivery technique involves drug consolidation in the niosomes to concentrate around the niosomes to the target region. Due to the ability of niosomes to demonstrate various types of medications inside their multi-environmental structure and furthermore because of different factors like cost, stability, and so on, they exhibit a structure similar to that of a liposome and can therefore be compared to elective vesicular frameworks as for liposomes. It is a more effective targeting agent because of these advantages over liposomes. For greater efficacy, the medication is administered by ophthalmic, topical, parenteral, and other routes to the site of action.

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