Ethosomes and Ethosomal Gel: A Novel Transdermal Drug Delivery System

Ajay Kumar, University Institute of Pharmacy, CSJM University
Shweta Verma, University Institute of Pharmacy, CSJM University, Kanpur

ABSTRACT:

The skin is the biggest and easiest to manage organ in the body. Systems for transdermal medicine distribution are made to pierce the stratum corneum. Several methods have been used to boost drug penetration rates. The most cutting-edge vesicular system, called ethanolsomes, has a high ethanol content that enhances drug penetration into the deeper layers of skin. The transdermal delivery of drugs is the main use of ethosomes. Transdermal drug delivery is a self-contained, distinctive dosage form that, when placed to the skin, gradually delivers the medication into the bloodstream. These carriers are designed to deliver drugs or therapeutic substances with precision. Ethosomal systems are theoretically difficult, yet they have an impact on how they are used. This article provides in-depth details on the ethosomal system, including the many types of ethosomes, including transethosomes, binary ethosomes, and classical ethosomes, according to their constituent parts. The study of vesicle-skin interaction considers evaluation criteria like vesicle shape, vesicle size and size distribution, zeta potential, percent entrapment efficiency, distinctiveness of permeation, surface tension measurement, physical stability, transition temperature, and surface tension measurement. This article discussed multiple ways to employ ethosomes to cure different diseases. Ethosomes offer a wide range of significant advantages, including raising medication effectiveness, enhancing patient comfort, and reducing total medical expenses. Topical medicines, which are often rubbed on the skin, have both regional and systemic effects. A topical gel is one of these products made for topical application. compositions that are semisolid and include a liquid-dissolved drug. They help with medicine distribution, which is why they are widely utilised. Gels are organic or synthetic three-dimensional (3D) structures that are connected by physical, chemical, or ionic interactions. Gels are divided into several groups based on their physical makeup, rheological properties, colloidal system features, and solvent system characteristics. The advantages of topical gels inspired the development of innovative techniques including hydrogel, emulgel, organogel, etc. Gels can be created in a variety of ways, including the cold process, applications, processes for gel formation, preparation methods, and evaluation standards.

KEYWORD- Hydrogel, emulgel, organogel, topical gel, and 3D structure are some related terms, Transdermal, ethanol, ethosomes, and vesicles. alcohol, ethosomes, ultrasound treatment, and lecithin.

INTRODUCTION:-

The skin, which is the easiest organ to govern and makes up around 15% of the adult body weight, is a constitutional organ. In addition to predicting water loss, it guards against somatic, chemical, and biological hazards coming from the outside. It is also necessary for thermoregulation(1). The epidermis, dermis, and hypodermis are the three layers that cover the skin. It is said that the stratum corneum, which makes up the epidermis, the skin's outer layer, acts as a tough barrier to stop drugs from penetrating the skin.This phenomenon restricts the rate at which the medication enters the bloodstream or is applied externally. Certain carriers are necessary to overcome the skin's barrier and deliver pharmaceutical molecules with various physicochemical properties into the systemic circulation.(2). (5).

A painless interface for systemic administration is provided by the transdermal distribution of medications and exogenous substances with therapeutic effect(3),(4),(5).The most recent method of drug delivery, which was developed in response to the rising demand for treatments with adequate patient adequacy, has many advantages over conventional drug

delivery, including lower drug dosages, improved patient compliance and convenience, and the prevention of gastrointestinal disturbances and first pass metabolism(6),(7).

Transdermal drug delivery systems are designed to disperse a therapeutically effective amount of medicine over a patient's skin over a prolonged period of time1.Over 40% of potential drug candidates are now undergoing transdermal delivery testing in clinical settings.(8) Novel vesicular carriers that ethosomes refer to as "soft vesicles" enable better dispersion to or through skin.(8)

Different sized ethosome vesicles are possible. Size range: 10 nm to microns. Ethanosomes are the modified liposomes that have a high ethanol content. The ethosomal system is composed of phospholipids, water, and ethanol.(8)

They have the ability to puncture the skin to enhance compound distribution to the body's deep skin layers. Ethanol is present in the ethosome. fluidizes ethosomal lipids and the intercellular lipid bilayer of the stratum corneum. The flexible, squishy vesicles pierce the lipid bilayers.(3), (4),(8).

Because it avoids the first pass metabolism that happens when oral drugs are given, giving antiemetic meds via the transmucosal route is a creative way to maintain blood concentration.administration. It also seems to increase patients' compliance with their treatment plans. Additionally, it could be beneficial for paediatric and elderly patients experiencing nausea and emesis.(11)

Studies on the effects of propranolol HCL ethosomal gel in drug administration through the buccal mucous membrane showed the gel's excellent capability and suggested that ethosomes should be included into hydrogels to increase bioavailability and improve medication delivery. By being added to gel, ethosomes may increase its stability and ability to penetrate the mucosa.This highlighted the superb compatibility between hydrogels and ethosomal carriers, improving their bioadhesive characteristics and enabling sufficient permeability for transmucosal drug delivery.(12)

The skin is the most accessible and adaptable route for delivering both systemic and topical medicines. The strongest resistance against drugs is provided by the stratum corneum, the top layer of the skin.(13,14,15)

Pharmaceutical penetration limits bioavailability when applied topically.It is crucial to research and assess the various carriers needed for systemic drug delivery in order to circumvent the natural skin barrier. Transdermal drug delivery, a less invasive form of pharmaceutical administration, guarantees controlled drug distribution, less frequent dosing, patient compliance, and avoidance of first pass metabolism.(13,14,15)

With the discovery of liposomes, drug transport research entered a new era, and several vesicular systems have since been created (16). Stretchable or flexible liposomes, also discovered in 1992 by Cevc and Blume, are known as transferosomes. After transferosomes, Touitou et al. published a ground-breaking investigation that resulted in the identification of a specific lipid vesicular system known as ethosomes.Modified liposomes were developed as a result of their decreased size, less effective entrapment, and negative zeta potential. Ethosomes are brand-new, modified lipid carriers made of ethanol, water, and phospholipids. In addition to phospholipids and water, ethanol is present in rather high quantities in ethosomes, which may improve their vesicular properties and skin penetration.(16,17,18,19,20,21,22) .

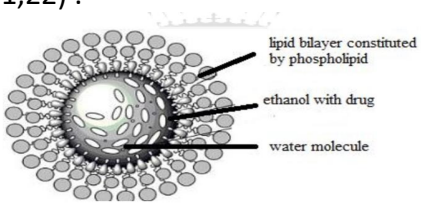

Figure no.1 ethosomes(114)

A topical formulation also has to be visually pleasant in addition to being physically and chemically stable[6]. Topical application is localised to the top layer of the skin and only affects the area to which it is applied. The use of topical medicines is intended to achieve the two major aims. The preservation and repair of the skin's natural barrier function is the primary outcome. The second outcome is an improvement in skin condition as a result of improving an active ingredient's effectiveness and skin delivery..(23,24)

PERKS OVER LIPOSOMES -Estisomes Provide A Viable Strategy For Improving Medication Delivery Through The Skin Due To Their Notable Advantages Over Liposomes(22,23,28). Over the past several years, a lot of research has been done on the benefits of ethosomes as drug delivery systems over conventional liposomes and ultraflexible liposomes, taking into account the following aspects.(22,23,28)

- In comparison to conventional liposomes, ethosomes transport active substances more efficiently across the stratum corneum and into deeper layers of the skin, where they are then retained.(27)
- When compared to ultraflexible liposomes containing a bilayer fluidizing agent like sodium cholate, compatibility with obstacles is shown to be superior.(27)
- When compared to liposomes and hydroalcoholic solution, ethosomal systems were shown to be superior in terms of extent and depth of medication and fluorescent probe delivery across the skin.(27)
- Ethosomes, as opposed to liposomes, might transport medications through the SC into deeper skin layers and potentially into the bloodstream.(27)
- In comparison to liposomes or the ethanolic drug solution, ethanolosomes are designed to increase the transdermal perviousness of loaded drugs.(28,29,3)

MERITS OF ETHOSOMES:

- Ethosomes are easy to use and safe for the skin.(27)
- Due to their ability to be produced in semisolid dose forms (Gel or Cream), ETHOSOMES give exceptional patient acquiescence in contrast to the drawbacks of iontophoresis and phonophoresis.(27)
- Since the toxicological description of ethosomalelements is finely endorsed in scientific literature, the ethosomal system does not abide any excessive scale drug development danger.(27)
- It has been demonstrated that the ethosomal vector may increase intracellular delivery of molecules with an affinity for both water and lipids as well as increase the penetration of an antibiotic peptide.(30,31,27)

DEMERITS OF ETHOSOMES-

- Because ethosomal formulation is intended for gradual and extended drug delivery, bolus type input cannot be accomplished with it.(27)
- The medicine needs to be sufficiently soluble in order to reach the cutaneous927) microcirculation and systemic circulation in both aqueous and lipid environments.(27)
- Drugs should have molecular sizes that are appropriate for transdermal administration.(27)
- Not all types of ski may be suited for adhesives.(27)
- Pricey(27)
- Yield will be quite low.(27)
- The potential for skin dermatitis or irritation as a result of the use of excipients such as permeation enhancers and other substances to improve medication delivery.(27)
- Product loss during the conversion of organic media to aqueous media(30,31,27)

Properties of gels:-

- It must be harmless, inert, and agreeable with other substances.(24)

- It ought to be practical both to use and to handle.(24)
- During storage, it need to keep its rheological properties.(24)
- It should not be oily and have thixotropic and emollient properties.(24)
- The topical gel shouldn't have a gummy texture.(24)
- The preparation's gelling agent should generate a consistency similar to that of a solid during storage and should be quickly degraded by shear forces produced by topical application, shaking the container, or squeezing the bottle.(24,32,33,34,35,36,37,38,39,40)

Characteristics of gel:

Structure- The networks that are created as a result of the interlinking of gelling chemicals are what give the gel its stiffness. The characteristics of the gel and the network's structure depend on the type of force and particle being used.(24)

Rheology:- The flocculated solids' dispersion and the gelling agents' solutions exhibit non-Newtonian flow behaviour because they are pseudo-plastic. When shear stress is applied to inorganic particles distributed in water, their fragile structure will be destroyed because having a stronger inclination to flow, to the breakdown of inter-particulate connection.(24)

Syneresis:- Numerous gels regularly spontaneously contract and release the fluid medium, a process known as syneresis. This results from the elastic strains that are created during the gel-setting process relaxing. Following the release of these tensions, the interstitial(24)

The solvent's accessible areas shrink, which causes the fluid to become visible.Hydrogels do not have this effect, but organogels, which are inorganic hydrogels, do. With a drop in polymer content, syneresis becomes more pronounced.(24)

Swelling:- A large amount of liquid is absorbed and the volume will grow if a gelling agent is kept in contact with the solvent (acting as the first stage of dissolution). We refer to this process as swelling. The solvent enters the process through theGel matrix substituting gel-solvent interactions for gel-gel interactions. The degree of cross-linking restricts swelling because it hinders breakdown.(24)

Aging:-Ageing refers to the process of aggregation that occurs more slowly in colloidal systems. As a result, a denser network of the gelling agent gradually forms.(24,33,34,35,36,37,38,39,40,41)

Structure of gels: A gel is made up of synthetic or natural polymers that form a 3D matrices across the dispersion medium. After being applied, the liquid evaporates, leaving the medication behind, which is subsequently bound in a thin layer of a matrix that forms a gel on the skin(41) (shown in Figure.No. 1).

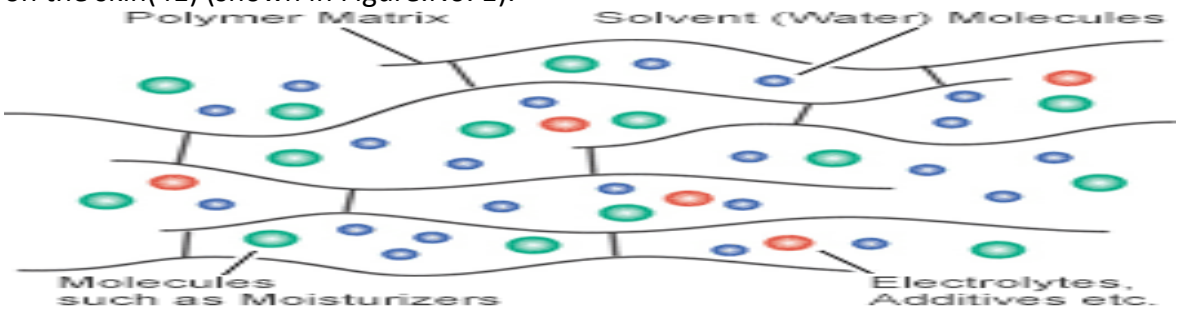

Figure No. 2: Structure of gel (drug being entrapped into the polymer)[24,(115)]

Networks are formed when gelling agents interact, and these networks are what give a gel its rigidity[36]. The sort of force used to establish connections and the composition of the particles used define the gel's structure and properties[42]. Whether or not the polymeric particles are spherical

The configurations of the particles can be shown in Figure 2 (a, b), whether they are isometric aggregates of tiny molecules or a single macromolecule. If the macromolecules are linear, the networks are created by the entanglement of relatively tiny molecules or molecules that are linked together in a crystalline structure, as seen in Figure 2(c,d).

The many forces involved in interlinking include the Vander Waals force, weak hydrogen bonds, and strong bonds. If the connections are due The melting of the gel is frequently triggered by the rise in temperature and weaker forces[38,42].

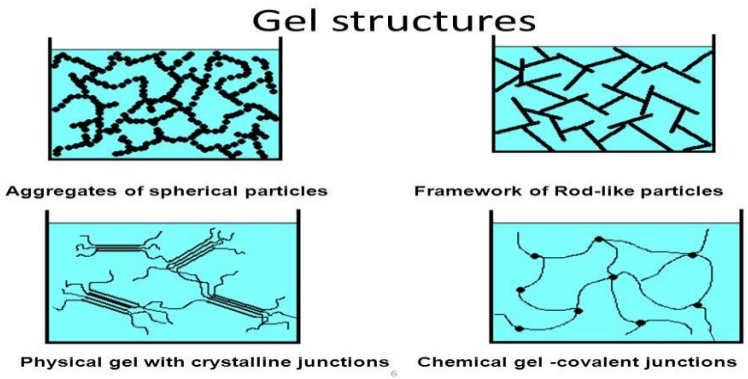

Figure No. 3

Classification of gel:

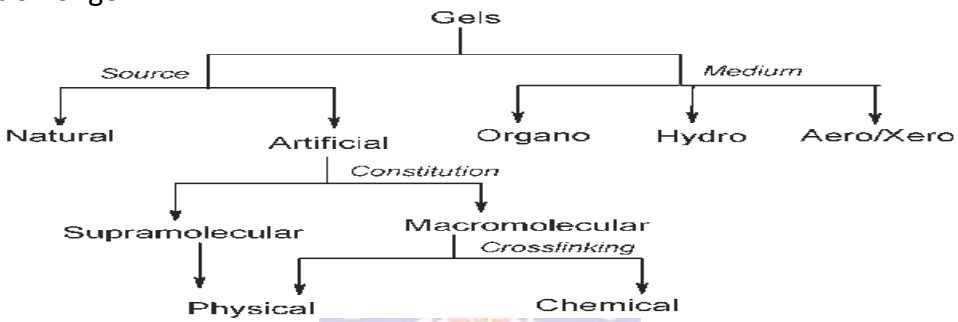

Figure.4(41,42,43)

Gel forming substances:

The following factors must be taken into consideration when choosing a polymer for topical preparations:

- They must be inert and not physically or chemically interact with the medicine.
- Should not be harmful.
- In the presence of the medicine and any excipients, it should be stable and not decompose.
- Should be utilised when loading a lot of medications.
- The characteristics of the molecular weight and chemi(44,32,35,36)

The following categories apply to polymers:

1. Natural polymers: These can be created by living things and can be found in nature.

Proteins include gelatin and collagen.

Tragacanth, Agar, Gillum gum, Alginic acid, Guar gum, Xanthine, and Cassia tora are examples of carbohydrates.

2. Synthetic polymers: These polymers are made in a lab setting called an in vitro environment. They are also known as synthetic polymers.

3. Carbomer, including Carbopol-940, Carbopol-934, and Carbopol-941; and Polyacrylamide the Poloxamer

Polyvinyl alcohol (d).

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Polyacrylamide (e).

f. Copolymers of polyethylene.

3. Semi-synthetic polymers: These are made by modifying natural polymers chemically. They include cellulose derivatives as a group.

Examples include carboxymethylcellulose, hydroxypropyl cellulose, hydroxyethylcellulose, and hydroxypropylethyl cellulose.

4. Inorganic polymers, such as aluminium and bentonite(45,41,42,35,36,44,32,24)

PREPARATION OF ETHOSOMES

Mechanical dispersion method:(46,27)

Soy PC was dissolved in Chloroform; Methanol mixture in 2:1 ratio in a wholly desiccated RB flask
Using rotary evaporator the organic solvent was detached (90 rpm – 15 min at 45°C)
A thin lipid film is obtained in the surface of flask which was kept under vacuum overnight to detach the traces of solvent
The dried film was hydrated using a hydroethanolic mixture in an orbital shaker (100-120 rpm – 1h) at room temperature
The formulation was sonicated (3 cycles – 5

Figure 5. Preparation of mechanical dispersion method

Soy PC + Permeation enhancer are dissolved in ethanol and pg (propylene glycol) in a concealed glass bottle (stirred at 1500 rpm)
The above mixture is heated up to 30°C in a water bath
Water is added to the prepared mixture and stirred continuously
Using a probe sonicator the above preparation is the sonicated (3 cycles – 10 min)
The formulation is stored in the refrigerator

Figure 6. Preparation of ethosomes by hot method

Soy PC is dispersed in water and placed in water bath at 40°C till a colloidal suspension is attained
Ethanol + PG (Popylene glycol) is heated at 40°C
The above mixture is added to the pospholipid mixture drop wise by continuously stirring (Mechanical or Magnetic stirrer
The drug is dissolved based on its hydrophilic or hydrophobic nature into either of the organic or aqueous phase
The preparation is the sonicated (3 cycles – 5 min at 4°C)
The preparation is homogenized using high pressure homogenizer (at 15000 psi) to get uniform nanosized ethosomes

Figure 7. Preparation of ethosomes by hot method

TYPES OF ETHOSOMAL SYSTEM(3

On the basis of their chemical makeup, ethosomes are divided into three categories.

Traditional ethosomes-

All that these ethosomes are, is modified liposomes. They are primarily made up of water, phospholipids, and ethanol at a high concentration (about 45% w/w). Due to their reduced size and improved entrapment effectiveness, these ethosomes were thought to be superior to liposomes for percutaneous distribution. Classical ethosomes performed better than liposomes in terms of stability and penetration. The traditional ethosomes were used to encapsulate drugs with MWs between 130.077 Da and 24 kDa.

Binomial ethosomes-

The binary ethosomes were first described by Zhou et al. The addition of an alcohol type to the conventional ethosomes allowed for the formation of these ethosomes. Isopropyl alcohol and propylene are the alcohols that are most typically utilised to create these binary ethosomes.

Transethosomes:-In the year 2012, Song et al introduced the transethosomes, a new generation of ethosomes. These ethosomes have the same components as traditional ethosomes, with the addition of a penetration enhancer or surfactant. These ethosomes were taken into account to enhance the benefits of the previously existing transferosomes, which are nothing more than deformable liposomes and traditional ethosomes combined

into a single transethosome formula. It is discovered that transethosomes are superior than traditional ethosomes. The inclusion of different edge activators or penetration enhancers improves the characteristics of the ethosomal system. Transethosomes can be used to encapsulate medicines with MWs between 200 and 325k Da and 130.077 Da(3,47,27).

Types of ethosomes

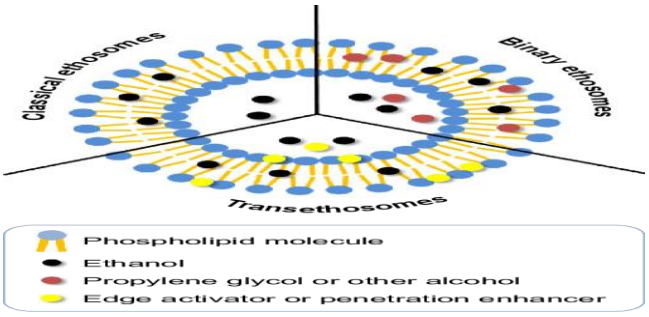

Figure.8Types of ethosomes

THE DRUG PENETRATION MECHANISM:

There are two likely paths in the stratum corneum, including intercellular and transcellular ones. Numerous divisors have an impact on how drugs are delivered into the skin by locally imposed vesicles. The deeper skin layers are significantly penetrated by vesicles that are smaller in size. The ratio of phospholipid to ethanol affects the size of ethosomes. The concentration of ethanol is shown to increase as the size of ethosomes decreases. Ethosomes enter the body through the skin's transcutaneous route, which is made up of the stratum corneum and open hair follicles. During transcutaneous permeation, the vesicles in the upper layer of skin are broken apart, allowing medicinal medicines to gradually penetrate the skin while the phospholipid is still present in the epidermis. This process is predicated on the mutually reinforcing actions of ethanol and fat to increase ethosome permeability. The stratified lipid Stratum corneum is organised and tightly packed at bodily temperature. Ethanol acts as an incursion enhancer, increasing the fluidity of the lipid layer and lowering the lipid density in the skin while also disrupting the organisation of the lipid bilayer. The use of ethanol makes the bi-layered vesicle flexible and ductile enabling simple skin penetration. The medicine will be ejected into layers of the skin that are deep upon amalgamation of these vesicles. As a result, using ethanol increases fluidity and may have ethosomal interactions with the vesicles and stratum corneum for more noticeable medication delivery(48,49).

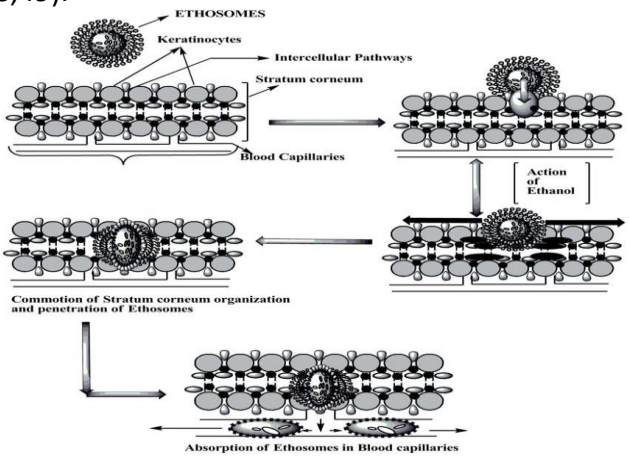

Figure no.9

ETHOSOME MECHANISM FOR THE SKIN DELIVERY

Drug permeation happens in two stages:

1. The impact of ethanol
2. The impact of ethosomes

Effect of ethanol-

Alcohol acts as a skin penetration booster. While the fluidity of the lipid cell membrane and insights into intercellular lipids are increasing due to ethanol, the density of the lipid multilayer in the cell membrane is decreasing.

Ethosome impact-

The permeability of skin increases when ethanol from ethosomes increases the fluidity of cell membrane lipid. Ethosomes penetrate deep into the skin's layers and combine with the lipids there, allowing the medicine to be released into the skin's deep layers(49,27,31).

There are 4 distinct ways to make a hydrogel, including:

Using UV light or a redox initiator system, solution polymerization or cross-linking involves polymerizing an ionic or neutral monomer with multifunctional crosslinking agents. The gels are cleaned after preparation to get rid of the letting it expand in the presence of water will allow it to absorb unreacted solvents, monomers, and initiators. The solvents employed in this procedure are ethanol, water, ethanol-water mixtures, and benzyl alcohol.(24,50,51)

When the amount of water utilised for polymerization exceeds the amount needed for swelling, heterogeneous hydrogels are created.The simplest method for making hydrogels is bulk polymerization, which uses vinyl monomers and an appropriate initiator. The kind of monomer and solvent employed will determine which initiator is used. the monomer's bulk polymerizationproduces a hard, glassy matrix that, when submerged in water, expands to become soft and pliable. UV light or a chemical catalyst can be used to cause polymerization.(24,50,51)

Radiation-induced polymerization: Unsaturated compound hydrogels are made by ionising them with high energy radiations like gamma rays and an electron beam that serves as an initiator.Radiation exposure to the aqueous polymer solution causes radicals to form onthe chains of polymers. Hydroxyl radicals are created by the radiolysis of water molecules, and they attack the polymer chain to form macro radicals. By forming covalent bonds, the recombination of the synthesised macro radicals on various polymer chains results in a cross-linked structure.(24,50,51)

Polyacrylic acid, polyvinyl alcohol, and polyethylene glycol are examples of polymers that can be utilised in this approach. This approach has an advantage over others since the hydrogels it produces are clean and devoid of initiators.(24,50,51)

Inverse-suspension polymerization, also known as suspension polymerization, is the process of employing the oil-in-water method rather than the water-in-oil (w/o) method. The hydrocarbon phase is mixed with the monomers and initiators until a homogenous mixture is produced. The agitation rate determines the particle size,viscosity, medium, and rotor design. The dispersion has to be suspended using a low HLB (Hydrophilic-Lipophilic Balance) system since it is thermodynamically unstable.(24,50,51)

representation of the procedures necessary to make emulgel[32,33,34,46,47].

1. Emulsion formulation with or without water

a. Making the oil phase: To make the oil phase, light liquid paraffin is dissolved in span 80 after the oily component has been dissolved in the emulsifier.

Aqueous phase preparation involves dissolving the aqueous part in the emulsifier, in this case, tween 80 is dissolved in filtered water.

c. Making the medication solution: The medication solution is made by combining the medication with ethanol.

Depending on the application, the medication solution is integrated into the aqueous phase or the oily phase.

solubility. After been heated before, both phases are combined with constant stirring and cooled to room temperature.

2. The preparation of the gel base involves mixing a polymer into purified water using a mechanical mixer. Utilising TEA, the gel's pH is brought down to 6-6.5.

3. Adding the prepared emulsion to the gel basis: Using glutaraldehyde, the created emulsion will be incorporated into the gel base in a 1:1 ratio.(52,24,53,54,55,56,57)
Mechanism of gel formation-
The gels are created by three different forms of cross-linking, including: 1) Ionic cross-linking, which results in the production of ionic bonds. The interaction of the charges on the polymer and the solvent leads to the formation of ionic bonds.
For instance, when calcium ions are present, polysaccharide alginate creates a gel that can encase enzymes.The usage of an example shows how a pH change may also result in gel: pectin creates gel when the pH is acidic[44].

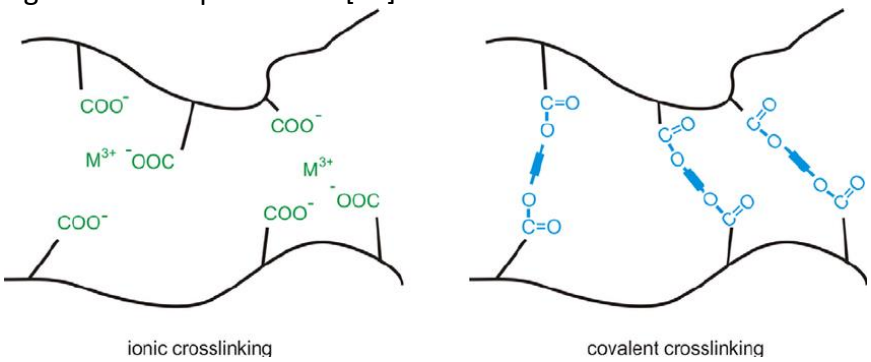

Figure No. 10 Ionic cross-linking(44)

Chemical cross-linking-

When two or more monomers are combined to form a polymer, a covalent connection is created between them that has a high molecular mass and is irreversible. These polymers are insoluble and only dissolve when a certain solvent is added.
causes the polymer to swell, producing gel. You may view chemical cross-linking .polymers with unbound or free groups in eir structure. Sangeetha S et al. They make the polymer more viscous because of the irreversible binding. Using an example, this may be demonstrated: Chemical cross-linking is created by polyacrylic acid with many carboxylic acid groups and glycols with hydroxyl groups.(44)
Physical cross-linking: Hydrogen bonds, the solubilization of the crystalline component, temperature changes, concentration changes, and hydrophobic contact can all lead to the formation of gels. These gels include cellulose gels, poly (N-isopropyl acrylamide) gel, and others.dextran gel (44)

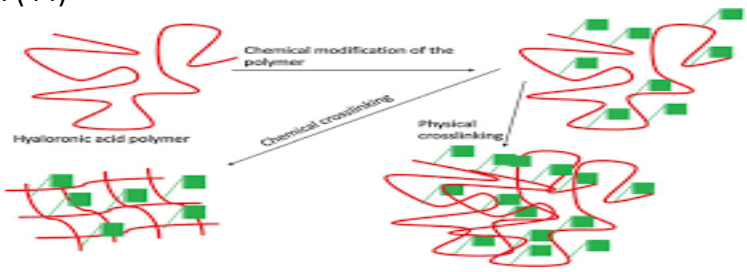

Figure No.11 Physical cross-linking](44).

ETHOSOME VALIDATION CRITERIA:

1. Vesicular Morphology

Transmission electron microscopy (TEM) and scanning electron microscopy (SEM), which stain the samples negatively with an aqueous solution, are used to examine the morphology of the ethosomal system. The solution of ethosomes was stained using a tiny carbon-coated grid. Blotting is used to remove the extra solution. After drying, it is seen using a TEM or SEM to look for vesicles(62, 63,24).

2. VESICLES' SIZES AND DISTRIBUTION OF SIZES:

Dynamic light scattering (DLS) and PCS (photon correlation spectroscopy) are typically used to evaluate vesicles in the ethosome formulation(64,24,49). The formulation's ingredients

have an impact on the range of diameters between microns and nanometers (58,59,60,61,24).

3. A certain percentage effectiveness OF ENTRAPMENT:

The extended release characteristics of ethosomes are endowed by the entrapment efficiency, which must be measured(24). The following methods are often used to calculate the entrapment efficiency:

Ultracentrifugation (3.1)

Dialysis (3.2)

Ultracentrifugation (3.1)

It consists of two segments, the first of which contains the vesicle preparation and is exposed to ultracentrifugation at the intended rpm and time. The second segment contains the pure drug, which is assayed using techniques like HPLC to determine the degree of entrapment using the formula shown below(37):

Entrapment effectiveness is EE.

Dt is theoretically equal to the amount of medication added.

Ds is equal to the amount of drugs in the supernatant.

Dialysis: Vesicles that are loaded with drugs are placed in the prepared dialysis bag, which is made of polymers like cellulose acetate and left in a saline solution for 1 hour to ensure that the membrane is completely wetted. The vesicles are then transferred to a 500ml solution of PBS (phosphate buffer saline) that has a pH of 7.0. The media are swirled using a magnetic stirrer, and the sink condition is maintained by removing aliquots of a same size from the medium receiving at regular intervals and replacing the PBS solution with an identical volume. Drug content of samples is evaluated by HPLC(49,65). Next, the entrapment efficiency is determined using the formulas above (66), (67), (69), and (68).

4. ZETA POTENTIAL: The development of charge between a liquid medium and its solid surface at the interface is known as the zeta potential, which may be measured using a zeta metre or a zeta sizer and is expressed in Milli Volts(70),(67),(68).

5. PERMEATION DIFFERENTIATION: The ability of ethanol to penetrate has long been recognised. Two effects are attributed to the penetration properties of which are enhanced by the creation of flexible ethosomal characteristics and are provided by the synergistic interaction between the lipids in skin, vesicles, and ethanol, demonstrating that the penetration enhanced by ethosomes is significantly superior to the penetration enhanced by ethanol alone. The following are the two results.

Push effect (5.1)Increasing thermodynamic activity as a result of ethanol vaporisation

Pull effect (5.2)The barriers in the skin's tissue are lessened by ethanol, which accelerates medication permeation(62,64).

6. MEASUREMENT OF SURFACE TENSION: A ring technique for determining the surface tension of a substance is the Du Novy ring tensiometer.(64,62)

PERSONAL STABILISATION:

Cholesterol plays a key role in the dispersion of ethosomes throughout the whole system throughout their formation, and aggregation occurs when cholesterol is absent. Because of the high level of ethanol in ethosomal formulation and the sensible amount of cholesterol that ensures its stability, cholesterol is discovered to be stabilised in the bilayer when ethosomes are preserved in the gel form. This flexibility of ethosomal vesicles is also made certain. Through the use of freeze drying, the stability of ethosomal suspension over an extended time of storage is guaranteed(66),(70).

The transition temperature is eight.The ethosomal system transition temperature is determined using differential scanning calorimetry(64).

9. THE SKIN - VESICLE INTERACTION STUDY:Using fluorescence microscopy, the relationship between the skin and vesicle may be investigated.(71,60)

Measures used to evaluate the topical gel-(33,34,35,36,38,45,42,39,71,72,73,74,75)

1. Physical assessment(33,34,35,36,38,45,42,39,71,72,73,74,75)
2. Calculation of pH(33,34,35,36,38,45,42,39,71,72,73,74,75)
3. elasticity(33,34,35,36,38,45,42,39,71,72,73,74,75)
4.Spreadability (33,34,35,36,38,45,42,39,71,72,73,74,75)
5. Study of extrudability(33,34,35,36,38,45,42,39,71,72,73,74,75)
6. Uniformity(33,34,35,36,38,45,42,39,71,72,73,74,75)
7. Roughness (33,34,35,36,38,45,42,39,71,72,73,74,75)
8. Reliability 9. Yield percentage (33,34,35,36,38,45,42,39,71,72,73,74,75) (33,34,35,36,38,45,42,39,71,72,73,74,75)
10. Drug use(33,34,35,36,38,45,42,39,71,72,73,74,75)
11. Research on in vitro diffusion(33,34,35,36,38,45,42,39,71,72,73,74,75)
12. Research on skin irritation(33,34,35,36,38,45,42,39,71,72,73,74,75)
13. Constancy(33,34,35,36,38,45,42,39,71,72,73,74,75)
15. Kinetic analysis(33,34,35,36,38,45,42,39,71,72,73,74,75)

I. Physical examination: The produced gels should be examined for their occlusive, washability, and organoleptic characteristics. (33,34,35,36,38,45,42,39,71,72,73,74,75)

II. Calculating pH: A digital pH metre will be used to measure the produced gel. meter. When storing the gel at 4 °C for approximately 2 hours, 1 g of the gel has to be dissolved in 100 ml of distilled water. Readings from the electrode should be recorded after dipping it in the diluted gel. Average results are documented and the measurements will be performed in triplicate. (33,34,35,36,38,45,42,39,71,72,73,74,75)

III. Viscosity: A viscometer will be used to measure the gels' viscosity. At each speed, the gels will be spun at 0.3, 0.6, and 1.5 RPM, and the values will be recorded. By multiplying the dial reading by the factor specified in the table, the viscosity of the gels will be calculated. (33,34,35,36,38,45,42,39,71,72,73,74,75)

IV. Spreadability is described in the of the Brookfield Viscometer Catalogue as the region to which the gel spreads easily when applied to the skin. The "slip and drag characteristics" of the gel, which may be described as the amount of time (in seconds) needed for the two glass slides to separate from the gel when positioned between the slides and facing the direction of the applied force, will be used to measure it. (33,34,35,36,38,45,42,39,71,72,73,74,75)

V. The produced gels will be placed inside the collapsible tubes for the extrudability investigation. The extrudability will be assessed in terms of the weight (g) necessary to extrude a gel ribbon of about 0.5 cm in length in 10 seconds. (33,34,35,36,38,45,42,39,71,72,73,74,75)

VI. Homogeneity: Based on appearance and the existence of any aggregates, the gels will be visually inspected to determine their homogeneity. (33,34,35,36,38,45,42,39,71,72,73,74,75)

VII. Grittiness: A light microscope will be used to determine it. The prepared gel is devoid of grittiness if there is no particle debris present. (33,34,35,36,38,45,42,39,71,72,73,74,75)

VIII. Consistency: A glass cup will be filled with the gel. A holding rod-mounted cone will be dropped from a height of around 10 cm in the direction of the glass cup's centre. From the gel's surface to the tip of the cone, the stabbing will be measured. which the gel contains. After 10 seconds, the cone's distance travelled will be reported. (33,34,35,36,38,45,42,39,71,72,73,74,75)

IX.Percentage yield: After weighing the empty container, the formulation is added. The weight of the full container will be subtracted from the weight of the empty container to get the practical yield. The formula below can be used to compute the percentage yield. (33,34,35,36,38,45,42,39,71,72,73,74,75)

X. Drug content: 100 ml of an appropriate solvent should be combined with 1 g of the produced gel before filtering. By appropriately diluting the stock solution, aliquots of various

concentrations will be created, and the absorbance will be measured. The following equation is created using linear (33,34,35,36,38,45,42,39,71,72,73,74,75) examination of the calibration curve using regression. (33,34,35,36,38,45,42,39,71,72,73,74,75)

XI. Studies on in vitro diffusion The Franz diffusion cell, which is mounted with a cellophane membrane, will be used to conduct the diffusion investigations. A certain quantity of the formulation will be present in the donor compartment. The receptor compartment, which contains phosphate buffer (pH 7.4) kept at 37°C, will be submerged in the donor compartment. The sample will be taken out of a predetermined amount of time, the receptor compartment. At each interval, the same volume of the fresh medium will be replenished after removing the sample. Phosphate buffer will be used as a blank to spectroscopically evaluate the drug concentration. (33,34,35,36,38,45,42,39,71,72,73,74,75)

XII.Skin: irritation tests are carried out on 400–500 g, either-sex Guinea pigs. The animal should be cared for according to industry standards. The hair will be shaved in an area of around 4 cm2 before the gel is applied.and labelled to make it simple to distinguish between the test and control groups. For seven days, a 500 mg/guinea pig gel will be administered twice daily. The location will undergo sensitivity reaction monitoring on a regular basis, and it will be assessed according to the norm for sensitivity reactions based on situations like mild patchy erythema, mild or moderate patchy erythema, and severe with or without edoema. (33,34,35,36,38,45,42,39,71,72,73,74,75)

XIII.Stability: The freeze-thaw cycle will be used to conduct stability experiments on the produced formulation. The product will be exposed to a range of temperatures for 1 month, including 4 C, 25 C, and 40 C, as well as ambient temperature. (33,34,35,36,38,45,42,39,71,72,73,74,75)

XIV. Kinetic analysis: Zero order can be used to calculate the release kinetics. The equations of Higuchi and Korsmeyer-Peppa. The decisions on how to interpret the data will be made in light of the comparison of the correlation coefficient and linearity.(33,34,35,36,38,45,42,39,71,72,73,74,75)

New methods for making topical gels:

1) Hydrogel: Hydrophilic gels are another name for hydrogels. They are the 3D crosslinked polymeric networks that can absorb roughly 10–20 times their own weight in water.
swelling and increases in molecular weight[21]. They may be chemically resistant or eventually dissolve and disintegrate. The hydrogels can be referred to as "reversible gels" or "physical gels" since they swell as a result of molecular entanglements and/or secondary forces of attraction like hydrogen bonds or ionic bonds. The hydrophilic functional group connected to the polymer backbone gives hydrogels their ability to absorb water; the cross-linkers between the particles give them their ability to resist disintegration. The hydrogel's water content enables the polymer acts as a matrix to keep the water together as the solute molecules dissolve[78,79].

2) Emulgel: Emulgels are essentially emulsions and gels together. They were created to deliver hydrophobic medications. Either an o/w or w/o emulsion can be used; o/w systems immediately entrap lipophilic medicines, whilst w/o systems do not.

3) encapsulate the medications that are hydrophobic[33,35,24]. One immiscible liquid is dispersed into another in the biphasic emulsion systems that the emulgels encounter. This causes stability problems that can be resolved by using emulsifying agents. The presence of fluid inside the structure of the gels contacting emulgels might cause them to swell[53,24].

4) Organogels are a type of viscoelastic system that contain an external non-polar phase that is immobilised. Through physical interactions amongst the gelators, this non-polar phase becomes immobilised inside the voids to create a 3D network[80,24]. Organogels can be utilised to deliver bioactive chemicals since they are often thermodynamically stable. Organogels are bi-continuous systems made up of non-polar solvent and gelators, which may or may not have water molecules trapped inside of them[81,24]. The creation of the 3D

structure may occur when the gelators are concentrated to 15%. The created 3D structure could stop the exterior phase from flowing[35,80,24].

5) SLN is a brand-new possible colloidal carrier technology. It is a solid lipid nanoparticle-based gel. They consist of a solid hydrophobic core covered in a monolayer of phospholipids that ranges in size from 10 to 1000 nm. Drugs that are both lipophilic and hydrophilic may be transported through the hydrophobic chains found in phospholipids.(82,83,84,24)

6) Liposome-based gel: Liposomes are phospholipid-rich concentric, bilayered vesicles that resemble shells. Topical liposomes are more efficient and much less harmful than oral liposomes. Both hydrophilic and lipophilic compounds can be employed with them. This gel can have a delayed and regulated release; as a result, patient compliance is improved.(82,85,24)

7) Solid dispersion-based gel: It is made up of two or more components, primarily a solid-state hydrophilic carrier and a hydrophobic medication. This method is mostly used to increase the solubility and bioavailability of drugs that are poorly soluble in water, such as when the solid Upon exposure of the dispersion to aqueous solutions, the medication is released as a result of the carrier's dissolution.(82,86,24)

8) Niosomes-based gel: Niosomes are small, non-ionic vesicles that range in size from 10 nm to 100 nm and are made of cholesterol. They can penetrate more effectively. Compared to liposomes, they are more stable.(82,24)

9) Gel containing microspheres: Microspheres are also known as micro-particles. They are typically tiny, spherical, free-flowing powders made of proteins or artificial polymers that are typically biodegradable. They range in size from 1 m to 1000 µm(35,24).

10) Gel that is based on microsponges: Microsponges are spherical, homogeneous, porous microspheres with multiple voids, with a particle size range of 5 m to 300 m. When a microsponge-based formulation is created and put to the skin, the drug's release may be managed through pH, wetness, diffusion, rubbing, and skin temperature.(24,35,82)

Ethotypical applications -

- Ethosomes for intravenous administration:
- Using ethosomes to transport DNA
- Delivery of hormones via ethosomes
- Transcellular delivery using ethosomes:
- Virus and microbial activities of ethosomes for skin infection:
- Ethosomes for fungal and viral infections
- testosterone-loaded ethosomes for hormone deficiency
- Testosome: ethosomal patch filled with testosterone
- testosterone ethosomal gel
- Ethosomes for menopause-related disorders
- Ethosome-based Parkinson's disease treatment
- Minoxidil-loaded ethosomes for treating hair loss
- Ethosomes with anti-inflammatory and anti-arthritic properties
- Using ethosomes during vaginal delivery
- Ethosomes with antipyretic and analgesic properties
- Skin disease treatment employing ethosome as a carrier
- ETHOSOES FOR HIGH BLOOD PRESSURE
- Applications of Ethosomes in Many Fields:

CONCLUSION:

The SC (stratum corneum) layer of skin serves as a significant barrier to the entry of drugs into the skin. Ethosomes are the cutting-edge vesicular system that is specifically designed and contains a significant amount of ethanol. This makes ethosomes flexible and dexterous enough to fluidize and intrude the lipids of the stratum corneum, which results in an

effective delivery of medication into the deeper layer of skin. In addition to the non-invasive administration of small, intermediate, or notably big molecules, low-cost treatment and patient compliance are also attained. Ethosomes provide improved therapeutics with new difficulties and opportunities. It is clear that researchers are very interested in these ethosomal vesicles and will approve medication release in vivo with them. Gel formulations have recently become more popular than other topical treatments due to its ease of washing, simple preparation process, stability, controlled release when compared to other preparations, patient acceptance, and less adverse effects. skips the digestive system, improves absorption, and boosts bioavailability. They increase medicine absorption while actively targeting and minimising adverse effects. effects. The gel compositions need to be improved to increase stability and effectiveness. Topical gels are quite safe and sound when utilised, according to recent studies.

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