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ADVANCEMENTS IN TOPICAL GEL FORMULATIONS FOR DERMATOLOGICAL APPLICATIONS

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ABSTRACT

Although they're easier to apply and have superior precutaneous absorption, topical gels are growing in popularity. Gels are formulations that are semisolid, immobilized inside the void of a three-dimensional network structure, and contain an external solvent phase. They can also be hydrophobic or hydrophilic. Comparing gel formulations to cream and ointments, the former offer superior stability and application properties. The primary route for topical drug delivery systems is the skin, which is one of the largest and easiest organs in the human body to access for topical administration. Topical gels are designed for application to the skin or specific mucosal surfaces in order to provide localized action, allow medication to penetrate through the skin, or provide emollient or protective properties. Other gel types-such as proniosomal gels, emulgels, bigels, and aerogels-for cutaneous medication administration have been reported in recent investigations. This review covers every detail pertaining to new methods of topical gel formulation, as well as the Advantages and categories of gel.

KEYWORDS: Emulgel, Topical gel, Hydrogel, Rheology, Gel formulation, Polymers, Qbd.

1. INTRODUCTION

A localized drug delivery technique, topical gel is meant to be applied topically to the skin, rectum, eye, or vagina. Any solid material that resembles jelly and can have characteristics ranging from soft and weak to rigid and tough is called a gel. Gels are semisolid formulations that are immobilized inside the gaps of a three-dimensional network structure. They contain an external solvent phase and can be either hydrophobic or hydrophilic in nature. Gels are

defined by the U.S.P. as a semisolid system composed of a dispersion of either big organic molecules or small inorganic particles surrounded and interpenetrated by liquid. The gel will have a fully transparent or opaque look. Most of topical gels are made with organic polymers, including carbomers, which give the product a clear, dazzling appearance and make it simple to remove with water from the skin. Gels are liquid-rich two-component semisolid structures.[1,2] A natural or synthetic polymer creates a three-dimensional matrix inside a hydrophilic liquid to form a typical polar gel. Natural gums including tragacanth, carrageenan, pectin, agar, and alginic acid are commonly utilized, as well as semi-synthetic materials like methylcellulose, hydroxypropylmethyl cellulose, hydroxyethyl cellulose and carboxymethylcellulose, as well as the synthetic polymer carbopol. certain clays, as long as the medication doesn't bond to the polymer or clay, like bentonite, veegum, and laponite. Gels find extensive uses in the culinary, cosmetics, biotechnology, pharmaceutical, and other industries.

The human skin is one of the largest and easiest organs to access for topical administration. It serves as the primary channel for the delivery of topical medications.[3] Drugs have a greater ability to absorb via the skin when they penetrate deeper. Topical treatments are used to treat the skin in order to achieve systemic, local, or superficial effects. Because of its medicinal qualities, such as its emollient, calming, or protecting action, the base may occasionally be used alone. On the other hand, a lot of topical medicines include medicinally active components that dissolve or disperse in the base. Comparing topical application to traditional dose forms reveals numerous benefits. Because of their bilayer structure and content, they are generally thought to be less hazardous and more effective than conventional formulations. An attempt is being made to use drug carriers that guarantee sufficient localization or penetration of the drug within or through the skin in the formulation of topical dosage forms, either to ensure appropriate percutaneous absorption or to maximize the local and reduce the systemic effects. Topical preparations boost the medicine's bioavailability, reduce GL-irritation, and stop the drug from being metabolized in the liver. The place of action is immediately affected by topical medicines.[1,4]

1.1 Properties of gels

a) It ought to be non-toxic, inert, and compatible with other additives.
b) Its application and handling should be convenient.
c) In storage conditions, it ought to be stable.

d) The drug's biological nature shouldn't be impacted.
e) A safe, inert gelling agent that does not interact with other formulation ingredients is ideal for usage in pharmaceutical or cosmetic applications.
f) It should have qualities like non-staining, thixotropic, greaseless, and emollientness, among others.
g) When exposed to shear forces produced by shaking the bottle while squeezing the tube, or applying topically, the gelling substance included in the formulation should provide an acceptable solid-like character that can be broken readily.
h) In order to guard against microbial attack, it should have an appropriate anti-microbial.
i) The topical gel shouldn't be tacky.[4]

1.2 Classification of gel

Gels can be categorized according to their physical characteristics, rheological qualities, solvent type, and colloidal phases.

1) Based on colloidal system

a) Inorganic two-phase system

If the dispersed phase's particle size is relatively large and forms a three-dimensional structure throughout the gel, the system's gel structure may not always be stable and instead consist of floccules of small particles rather than layer molecules. Such as Aluminum Hydroxide Gel USP.

b) Organic single-phase system

These are made up of big organic molecules that are dissolved in a continuous phase and reside on twisted supports.

For example, tragacanth, carbopol

2) Depending on the type of solvent utilized

a) Hydrogel

In this instance, water is present in their continuous liquid phase.

E.g., Gelatin, cellulose derivatives, Bentonite magma and poloxamer gel

b) Organic gel (Solvent not aqueous)

These have a continuous phase of a non-aqueous solvent.

For example, plastibase (low molecular weight polyethylene dissolved in mineral oil and quickly cooled), Olag (aerosol) gel, and metallic stearate dispersion in oils.

c) Xerogels

Examples of xerogels include dry cellulose, polystyrene, acacia tear β-cyclodextrin, tragacanth ribbons, and solid gels with low solvent content that are created by solvent evaporation or freeze drying.

3) Based on rheological characteristics

Non-Newtonian flow features are typically seen in gels. They fall into the following categories:

a) Plastic gels

For instance, Bingham bodies and flocculated suspensions of aluminum hydroxide show a plastic flow, and the rheogram plot indicates the gels' yield value-the value over which the elastic gel deforms and starts to flow.

b) Pseudo plastic gels

For instance, pseudo-plastic flow is seen in the liquid dispersion of tragacanth, sodium alginate, Na CMC, etc. These gels have no yield value and their viscosity falls as the rate of shear increases.

c) Thixotropic gels

These gels have extremely weak particle connections that are easily disrupted by shaking. The particles will collide and bind together once more, causing the resulting solution to return to gel. such as agar, bentonite, and kaolin.

4) Based on physical state

a) Rigid gels

This can be created from a macromolecule with a primary valence bond linking the framework. For instance, silica gel is a polymer structure with a network of pores because silic acid molecules are bound together by Si-O-Si-O bonds.

b) Elastic gels

Gels are Agar, pectin, guar gum, and alginates gels behave elastically.[3,4]

2. Methods of preparation of gel

a) Cold method

Using a low temperature of roughly 50C, all of the ingredients were combined to create a homogenous mass in this way. In this case, the medication and solvent are combined to make solution B after the polymer and penetration enhancer are combined to form solution A. Subsequently, mix continuously while adding solution B into solution A.

b) Dispersal method

This method involves dispersing the polymer over water for two hours, allowing the polymer to become completely soaked in water. Next, the additional ingredients are added, stirring continuously until a homogenous mass is created.

c) Chemical reaction

By using this approach, the solute and solvent interact chemically to generate gel. such as the planning of aluminium hydroxide with silica gel.

d) Temperature effect

The solubility of most lipophilic colloid, such as gelatin and agar, decreases with decreasing temperature. in order to produce concentrated hot sol gel when cooled.

e) Flocculation

Using this approach, gelatin is made by adding just enough salt to cause a precipitate that results in an aging state, but not enough to cause full precipitation.[4]

3. Evaluation parameters of topical gel

a) pH of the gel

A digital pH meter was used to determine the gel's pH. After dissolving 1 gram of gel in the medium, use a pH meter to check.

b) Appearance and Homogeneity

Visual inspection was used to assess the homogeneity and physical appearance.

c) Viscosity

The Brookfield Viscometer was used to determine the gel's viscosity.

d) Spreadability

A second glass plate was placed over the pre-marked circle of 2 cm in diameter, on which 0.5 g of gel was applied. For ten minutes, a 500 g weight was left to rest on the upper glass plate. It was observed that the diameter had increased as a result of gel spreading.

e) Extradurability

In order to gauge extradurability, the creased end of a closed, collapsible tube filled with gel was firmly squeezed. Gel ejected till the weight dispersed at the moment the cap was removed. The weight in grams needed to release a 0.5 cm gel ribbon in 10 seconds was calculated. It was stated what the typical expulsion pressure was in g.

f) Skin irritation test

For the skin irritation test, a breed of Swiss albino mice was utilized as an animal model, together with 400–500gm of either sex Guniea pigs. After using a skin removal cream to remove the hairs, the skin is cleaned with spirit. Three mice are utilized, and the animals' levels of irritation are assessed after applying blank gel, normal saline, and formulation.

g) Stability studies

The gel underwent a stability study in accordance with ICH recommendations. It was stored at 30°C± 2°C/ 60% ± 5% RH and 40°C± 2°C/ 75% ± 5% RH. The formulation's changes in viscosity, pH, spread ability, and physical appearance were examined.

h) In vitro diffusion studies

i) Topical gel Disintegration and Release are studied using Franz diffusion cells. A 0.5g gel sample was placed in a membrane, and the dissolution process was conducted at 37 ± 1°C using a 250ml phosphate buffer with a pH of 7.4. Withdraw the 5 ml sample every 1, 2, 3, 4, 5, 6, 7, and 8 hours. Replace each sample with an equal volume of new buffer solution. Use phosphate buffer as a blank reagent for analyzing the sample in a spectrophotometer.

j) Drug content: Take 1g of gel, dissolve it in 100ml of appropriate medium, and filter the mixture to find the drug content of the gel. Following spectrophotometer examination of the filtrate, absorbance is determined, and regression linear analysis of the calibration curve is used to determine the drug content.[5]

4. Novel approaches for gel formulation

4.1 Emulgel

Emulgels are emulsions combined with gels. Emulgel has shown promise as a medication delivery method for hydrophobic medicines. Because polymers have the ability to gel, they can be used as thickeners and emulsifiers. This is because they can create stable emulsions and creams by reducing surface and interfacial tension while simultaneously raising the aqueous phase's viscosity. In actuality, an emulgel is created when a gelling ingredient is present in the water phase of a conventional emulsion. These emulgels offer significant advantages over both traditional and new vesicular systems in a number of areas. In actuality, an emulgel is created when a gelling agent that is present in the aqueous phase transforms a classical emulsion. Different medications can be applied topically to the skin using o/w and w/o emulsions. Thixotropic, greaseless, readily spreadable, emollient, easily removable, nonstaining, bio-friendly, long shelf life, bio-friendly, clear, and aesthetically beautiful are just a few of the advantageous qualities of emulgels for use in dermatology.[6,7]

Additionally, because emulgels combine the benefits of emulsions and gels, they have a high patient acceptability rate. High diffusion and absorption rates, optical clarity, ease of preparation, and these attributes are present in emulgel formulations made from carbopol and HPMC.[36] Microemulsions have acceptable physical characteristics, drug release, and low skin irritation.[35,39,40] They also lower the stratum corneum's diffusion barrier.[37,38] Moreover, emulgels have demonstrated their promise as a great carrier for skin care products that offer UVA/UVB radiation protection.[41] Microemulsion-based gels (MBGs) have attracted a lot of attention lately as a possible topical drug delivery system for skin.[42-48] Since these gels are made of emulsions (Oil and Surfactant), they can be categorized as emulgels; yet, because of the smaller particle sizes, they are more stable than emulgels. Gelatin is created when a gelling ingredient is dissolved in a heated w/o or o/w microemulsion and subsequently chilled. Microemulsions have several benefits, one of which is their thermodynamic stability. Gels based on microemulsions therefore seem like a viable method of topical transdermal medication administration. Furthermore, topical medication administration on the skin has been studied for MBGs comprising PEG-8 capric glycerides and polyglyceryl-6 dioleate as surfactants and carbopol and xanthan gum as gelling agents.[37,49] It has been found that lecthin-containing microemulsion organogels based on isooctane or cyclohexane increase permeability rates through excised human skin by a factor of ten when compared to control solvents.[44]

Additionally, a range of oils and surfactants that are approved by pharmaceuticals can be used to create microemulsion-based organogels, such as isopropyl myristate[50,51] and Tween 80 and 20. MBGs can be utilized to solubilize hydrophilic medications and vaccines in addition to hydrophobic items in the continuous oil phase[36] because they include percolative electroconductive channels. Emulsion-based gels have also benefited from the introduction of nanotechnology, which has decreased particle size to nanoscale and increased skin penetration and stability.[50]

Advantages

- Transport of hydrophobic medications
- Minimal preparation expenses
- Improved stability and loading capacity
- Emulgels used to extend the effects of medicines with short half life
- Possible self-medication
- There's no need for intense sonication
- First pass metabolism is avoided.
- Delivery of drugs specific to a site
- Boost adherence from patients

Disadvantages

- Certain medications have poor skin permeability
- Large-particle pharmaceuticals are difficult to absorb through the skin
- Bubble formation during emulgel preparation
- Skin irritation or allergic response on contact dermatitis.[8]

Essential components in the emulgel preparation

1. Aqueous material

This creates the emulsion's aqueous phase, which includes elements like water and alcohol.

2. Oils

These substances comprise the oily phase. Mineral oils are commonly employed in topically applied emulsions, either by themselves or in conjunction with soft or hard paraffin, for their occlusive and sensory properties as well as as the drug's vehicle.

3. Emulsions

Emulsifying compounds are used to control stability during a shelf life that can range from days for spontaneously generated emulsions to months or years for commercial preparations, in addition to promoting emulsification during the manufacturing process. For instance, sodium stearate, Span 80, Tween 80, and stearic acid.

4. Gelling Agent

These substances are utilized as thickening agents as well as to improve the consistency of any dosage form. such as HPMC, Carbopol and Gelatin.

5. Permeation enhancers

These substances cause a transient and reversible increase in skin permeability by partitioning into and interacting with skin components. For example, 1% oleic acid and 5% lecithin.[6,8]

4.2 Hydrogel

Cross-linked polymers that absorb a lot of water without dissolving are known as hydrophilic gels, or hydrogels. Hydrogels are special materials because of their softness, intelligence, and ability to hold water. Cross-links between network chains give hydrogels their resistance to breakdown, while hydrophilic functional groups connected to the polymer backbone give them the ability to absorb water. While the polymer acts as a matrix to keep the water together, some solute molecules can freely diffuse through the hydrogel's water. Hydrogels possess an additional feature: the gel is a single polymer molecule, meaning that its network chains are joined together to create a single, large molecule at the macroscopic level. On the macroscopic scale of hydrogel samples, it is reasonable to anticipate that the conformational shifts of the elastically active network chains will become apparent. There is a state called gel that is halfway between liquid and solid. Several intriguing relaxation behaviors that are not present in either a pure solid or a pure liquid are brought about by these half liquids and half solid qualities. Hydrogel products include contact lenses, bandages, and superabsorbents.[9]

Diffusion and chemical stimulation are two different ways that drugs can be released from hydrogels. Movement across the polymer matrix or the hydrogel's bulk erosion control diffusion. Chemically triggered gels efficiently open their pores to release the medication that has been captured when they swell in response to external stimuli such as pH and temperature or by an enzyme action. Only sick tissues can benefit from the focused medication release provided by this kind of mechanism. Whereas chemical stimulation has found greater use in

oral drug delivery and can provide control for selective therapy, diffusion-based drug release is more frequently used for localized and non-specific drug release.[52,53]

Recent developments in hydrogel technologies have led to a rise in the use of hydrogels in the biomedical sciences, including controlled drug delivery, tissue repair, and cell encapsulation. Numerous innovative hydrogel-based delivery matrices have been developed and produced in response to the growing demands of the medical and pharmaceutical industries.[54,55] Furthermore, acrylated poloxamine hydrogels have been studied for tissue engineering and medication delivery.[56] A contemporary trend in gel technology is the investigation of polymerized oligolactides[58] and poloxaminehydrogels[57] as a delivery system for hydrophobic medications and bioactive compounds. Moreover, due to their poor solubility following oral absorption, chitosan hydrogels have been investigated as viable candidate vehicles for localized drug administration of medications with bioavailability issues.[53]

Additionally, the utilization of chitosan hydrogels in the transport of the active s-enantiomer of racemic propranolol.[59] and the berberine alkaloid has been investigated. Hydrogels, like heparin, are difficult to permeate the skin. Nanotechnology has been instrumental in the transdermal distribution of these difficult-to-penetrate molecules.[60,61] Researchers continue to focus on wound healing and anti-scar activities despite the abundance of previous research in these areas. Numerous medicinal compounds, including triamcinolone acetonid, curcumin, and astragaloside IV, have been included into hydrogels to promote effective wound healing. The hydrogels based on astragaloside IV shown both inhibitory efficaciousness against scar complications and angiogenetic effects on wound healing. Additionally, it supported collagen organization in adult tissues by preserving the type III/type I collagen ratio, which produced anti-scar activity.[62]

Advantages

- Low toxicity results from microbial organisms being trapped within polyurethane hydrogel beads.
- Hydrogels that are sensitive to changes in pH, temperature, or metabolite concentration can sense these changes and release their load accordingly.
- Natural hydrogel materials, such as agarose, methylcellulose, and other naturally generated polymers, are being researched for use in tissue engineering.
- Biocompatible

- Easy to modify

For the purpose of creating topical hydrogels, the drug's desired physicochemical characteristics are as follows

- The drug's molecular weight should be less than 500 Daltons.
- The drug needs to be sufficiently hydrophilic.
- A medication in a saturated aqueous solution should have a pH of five to nine.
- Topical administration of very acidic or alkaline drugs is not recommended.[9]

Methods used to produce hydrogels

1. Employing crosslinkers
2. Ultra-high pressure isostatic (IUHP)
3. Application of substitution reaction nucleophile
4. Using a gelling agent
5. Irradiation and freeze-thaw techniques
6. Industrial hydrogel synthesis

4.3 In situ gel

In recent years, in-situ forming polymeric gelling systems have gained popularity among novel drug delivery systems (NDDS) because of benefits like longer-lasting and sustained drug action, better patient compliance, and less frequent drug administration when compared to conventional DDS. This particular kind of mucoadhesive DDS gelates into a gel after coming into contact with bodily fluids. The polymeric formulation is in sol form prior to injection. This DDS is more palatable since it contains a variety of naturally occurring, biocompatible, biodegradable, and water-soluble polymers, including glycoginic acid, chitosan, poly-caprolactone, xyloglucan, poly-D, gellan gum, L-lactic acid, pluronic F127, carbopol, poly-D, L-lactide-co-glycolide, and pectin.[10,11,12]

Importance of in situ gelling system

1. The in-situ gelling system is important because: 1. Its in-situ forming polymeric delivery technology makes patient compliance and comfort better, reduces administration frequency, and is easier to administer.
2. The rapid precorneal drug clearance caused by the poor bioavailability and therapeutic responsiveness of conventional ophthalmic solutions can be mitigated with the use of gel

systems, which are infused as drops into the eye and undergo a sol-gel transition from the instilled dose.

3. The best dose form is a liquid that can both maintain medication release and stay in touch with the cornea of the eye for a long time.
4. Some negative side effects could arise from decreased systemic absorption of the medication discharged through the nasolacrimal duct.[12]

The ideal properties of polymers

The following qualities of a polymer used in in situ gels should be present:

- It should be biocompatible.
- It must possess the ability to stick to mucous.
- It ought to exhibit pseudoplastic behavior.
- Optical activity and tolerance should be satisfactory.
- It ought to affect the way tears behave.
- The polymer ought to possess the capacity to reduce viscosity when shear rate increases, hence providing decreased viscosity during blinking and stability of the tear film during fixation.[10,11]

Evaluation and Description of the in-situ gel system

- Texture analysis
- Clarity
- Gelling time and Sol-Gel transition temperature
- Viscosity and rheology
- Gel strength

4.4 Microemulsion based gel

An innovative method for topical medicine or medication administration is microemulsion. Microemulsions are multicomponent fluids with a diameter of 10–140 nm that are isotropic, thermodynamically stable, and consist of water, oil, surfactants, and/or cosurfactants. Compared to other ointments, drug transfer from microemulsion is better documented. One significant outcome is that, in comparison to traditional hydrogels, the stability of microemulsion-based gels (MBGs) is significantly higher. Another explanation for this is that the MBGs are made from thermodynamically stable w/o microemulsion systems, and the organic solvent used as the exterior phase may provide a higher level of resistance against

microbial contamination than the aqueous phase. Furthermore, the MBGs can be employed as a type of sustained release drug delivery system because the addition of gelatin to the W/O microemulsion increases the viscosity of the system. The MBGs' electrical conductivity, which can be used in iontophoretic drug delivery systems, is another feature that makes them appealing as drug delivery vehicles.[7,13]

Advantages

- Enhanced absorption rate
- Remove absorption variability
- Aids in solubilizing lipophilic medication
- Higher bioavailability.
- The drug moiety is quickly and effectively absorbed.
- Reduced energy use.[14]

Preparation techniques

- Phase inversion method
- Phase titration technique
- Microemulsion assessment

Evaluation of microemulsion

- Studying phase behavior
- Measuring viscosity
- Nature isotropic.[13,14]

4.5 Solid lipid nanoparticles based gel

Colloidal particles with a size range of 10–1000 nm is known as nanoparticles. Nanoparticles are made from synthetic and natural polymers, which are perfectly suited to maximize drug delivery and minimize toxicity. They have become a viable alternative to liposomes as drug carriers over time. The efficacious application of nanoparticles in drug administration is contingent upon their capacity to permeate several anatomical barriers, exhibit sustained release of their constituents, and maintain their nanoscale stability. Lipids have been proposed as an alternate carrier to circumvent these drawbacks of polymeric nanoparticles, especially for lipophilic drugs. These lipid nanoparticles are referred to as solid lipid

nanoparticles (SLNs), and formulators from all over the world are becoming increasingly interested in them.[15]

Advantages of solid lipid nanoparticles

- Shows enhanced and improved bioavailability of compounds that are not very water soluble.
- Dermal application for improved drug penetration into the skin
- Site-specific drug delivery
- Scaling up potential.
- Safeguarding sensitive molecules from the external environment and chemically labile substances from being broken down in the stomach
- Their stability surpasses that of liposomes.
- Boost the chemical synthesis of labile integrated compounds and increase the bioavailability of entrapped bioactive substances.
- Achieved was a high concentration of functional component.[15]

Preparation techniques for SLNs

1. Homogenization method

A. Hot homogenization

B. Cold homogenization

2. The method of solvent evaporation
3. Diffusion-emulsification of solvents
4. The approach based on microemulsion
5. The supercritical fluid technique
6. The technique of spray drying
7. The double emulsion approaches
8. The technique of precipitation
9. Dispersion of ultrasonography in films
10. Ultrasonication method after high-speed homogenization.[15]

Evaluation of solid lipid nanoparticles

- Particle Size and Zeta potential
- Physical characterization
- Diffusion

- Surface charge

4.6 Ethosomes based gel

The well-known liposome drug carrier has been slightly modified to create etherosomes. Phospholipids, water, and relatively high concentrations of alcohol (ethanol and isopropyl alcohol) are found in lipid vesicles called etherosomes. Soft vesicles called etherosomes are composed of water, phospholipids, and ethanol (in larger amounts). Ethamomes vary in size from microns (μ) to tens of nanometers (nm). They have a substantially higher transdermal flux and penetrate the skin layers more quickly.[16,17]

Advantages of ethosomes

- Enhanced drug molecule penetration to and through the skin to the systemic circulation
- Ethosomes, as opposed to typical liposomes, enhance drug delivery to the skin in both occlusive and non-occlusive scenarios.
- Ethamomes' safe composition and components make them useful in the fields of cosmetics, veterinary medicine, and pharmacy.
- Increased adherence from patients.
- Superior durability and soluble nature of numerous medications in contrast to traditional vesicles.
- Comparatively smaller in size than traditional vesicles.[18]

Limitations of ethosomes

- Low yield
- If shell locking is not successful, the ethosomes may agglomerate and disintegrate when they are transferred into water.
- Product loss that occurs while moving from organic to water media.

Methods for preparing ethosomes

1. Hot technique
2. The cold technique

Properties of ethosomes

- Visualization
- Measurements of surface tension activity
- Entrapment efficiency

- Vesicle size, and Zeta potential
- Transition Temperature
- Stability of Vesicles.[18]

4.7 Liposomes based gel

In a number of fundamental sciences, liposomes have proven to be a feasible substitute in a number of applications and a promising new medication delivery method. Liposomes are a type of microscopic vesicle that have an aqueous volume completely surrounded by a membrane made of lipid molecules and lipid bilayer structures. Since liposomes can be employed as drug delivery systems for regulated drug distribution for various therapeutical objectives, as well as carriers for hydrophilic and lipophilic compounds, they provide numerous benefits. The protection that liposomes provide as an encapsulating agent from potentially harmful circumstances in external surroundings is a significant feature of these particles. Liposomes can be applied topically to the skin and function as a local depot, penetration enhancer, and solubilizing matrix for poorly soluble medications, all while reducing their adverse effects. Topical liposome compositions may outperform traditional formulations in terms of effectiveness and toxicity. In comparison to standard formulations, liposome gel formulations may exhibit superior therapeutic benefits. This could result in enhanced patient compliance and longer and controlled release topical dosage forms. In addition, liposomes are a significant system unto itself in industrial, medicinal, and cosmetic uses.[19]

Advantages

- It is possible to avoid precipitation in the bloodstream and at the injection site.
- One of the rare solubilizers that is well tolerated intravenously is phospholipid.
- Assign specific passive targeting to the tissues of tumors
- Boost the therapeutic index and safety.
- Boost stability through encapsulation
- Effect of site avoidance.
- Reduces the encapsulated drugs' toxicity

Drug criteria for topical liposomal drug delivery system

- The list of medications that meet the requirements for the topical liposomal drug delivery system includes those that, when applied topically, are known to cause serious side effects. Such as glucocorticoid topical medication.
- Certain chemicals are typically ineffective when applied topically. For instance, interferon.
- Certain medications only exhibit inadequate results when used topically. For example, Hamamelis distillate.
- Medications that, when applied topically, exhibit a local irritating effect and trigger flare-up reactions early in the course of treatment, such as Retinoid (Tretinoin).
- Medication that needs to be applied for a long time and at high concentrations in order to relieve uncomfortable feelings that are frequently connected to dermatological conditions or their treatment, such as local anesthetics (Tetracaine).[19]

Methods of preparation of liposome

- The method of mechanical dispersion
- Method of solvent dispersion
- Method for removing detergents

Characterisation of liposomes

- Distribution of sizes
- Entanglement effectiveness
- Determining zeta potential (z)
- Studies on drug deposition and skin penetration
- Alternating tension sweep studies on rheology
- Frequency oscillation sweep
- Drug content and consistency of content.[19]

4.8 Solid dispersion based gel

A collection of solid goods made up of at least two distinct components-typically a hydrophilic matrix and a hydrophobic drug—is referred to as a solid dispersion. There are two types of matrix: crystalline and amorphous. The medication may be distributed crystalline, amorphous, or molecularly in the form of clusters. The quantity of medication candidates that are poorly soluble has skyrocketed in recent years. For formulation experts,

the formulation of medications that are poorly soluble for oral delivery poses a difficulty. A drug's solubility and/or dissolution rate determine its oral bioavailability, and dissolution may be the rate-determining step for the start of therapeutic activity. Over time, a number of techniques, including inclusion complexation, salt formation, and solvent deposition, have been developed to improve drug dissolution. Solid dispersion (SD), which was first used in the early 1970s, is one technique that works well for boosting the pace at which poorly soluble medications dissolve, hence increasing their bioavailability. One method used to enhance the dissolving of medications that are poorly soluble and whose absorption is limited by the dissolution rate is solid dispersion.[20]

Advantages of solid dispersion

- Enhanced surface area and dissolving rate due to smaller particle sizes. The end consequence is an increase in bioavailability.
- Enhanced wettability leads to higher solubility, Carriers are essential to improving Higher degree of particle porosity (wettability).
- The medication release profile is accelerated by the solid dispersion particles' enhanced porosity. The carrier characteristics also affect increased porosity.
- Drugs are shown as supersaturated solutions in solid dispersions, which are thought to be metastable polymorphic forms. Therefore, administering drugs in an amorphous form increases the solubility of the particles.
- Quick dissolving rates lead to a rise in the drug's absorption rate and extent.

Methods of preparation of solid dispersion

- Method of evaporating solvents
- Extrusion using hot melt and fusion process
- Physical blending
- Kneading method
- Supercritical fluid technology

Evaluation and Description of solid dispersion

- Outward manifestation
- Ratio of Practical Yield
- Studies on aqueous solubility
- Drug content

- Dissolution Research
- Compatibility of drug carriers

4.9 Microsphere based gel

Microspheres are tiny, spherical particles with dimensions between 1 and 1000 μm, or micrometers. Microparticles are another name for microspheres. The microspheres are naturally biodegradable particles made of proteins or artificial polymers that flow freely. Two are present. Many forms of microspheres;

- Microcapsules
- Micromatrices

The material that is imprisoned in microcapsules is clearly encircled by a distinct capsule wall, but in micromatrices the material is diffusing throughout the matrix of the microspheres. When a medication is added to solid biodegradable microspheres, it may release the medicine under controlled circumstances after being dissolved or distributed across a particle matrix. They are constructed from waxy, polymeric, or other protective compounds (Such as modified natural goods and biodegradable synthetic polymers).[21,22]

Advantages

- Microspheres have a long-lasting and consistent therapeutic impact.
- Reduces the frequency of doses, which enhances patient compliance.
- The spherical form and smaller size of these particles allow them to be injected into the body.
- More effective use of the medication will increase its bioavailability and lessen the frequency or severity of side effects.
- The shape of microspheres permits a regulated degree of diversity in medication release and breakdown.[23,24]

Disadvantages

- The controlled release dosage form's release rate can be affected by many factors such as food and the speed at which it passes through the stomach, resulting in a changed release from the formulations.
- Variations in the rate of release between doses.

- Controlled release formulations often have a larger drug load; hence, any compromise in the dosage form's release properties could potentially be hazardous.
- These kinds of dosage formulations shouldn't be eaten or crushed.[21,23]

Method of preparation of microspheres

- Ionic gelation
- Emulsion solvent evaporation technique
- Emulsion-solvent diffusion technique
- Emulsion cross linking method
- Multiple emulsion method
- Spray drying technique
- Coacervation method
- Hydroxyl appetite (HAP) microspheres in sphere morphology.[21,22]

Evaluation parameters

- Angle of contact
- Entrapment efficiency
- Particle size and shape
- Isoelectric point
- Density determination
- Swelling Index
- In vitro study.[22,25]

4.10 Niosome based gel

A non-ionic liposome based on surfactants is called a niosome. Cholesterol is used as an excipient in the formation of niosomes. You can utilize different excipients as well. Niosomes are more able to penetrate than earlier emulsion formulations. Although they have a bilayer and resemble liposomes architecturally, niosomes are more stable due to the materials employed in their creation, which gives them many additional benefits over liposomes. Niosomes are little particles that have diameters between 10 and 100 nm.[26]

Advantages

- The reason better patient compliance than with oily dosage forms because the vesicle solution is a water-based medium that may hold medication molecules with varying degrees of solubility.
- The formulation of the vesicle has adjustable and variable features.
- The regulated release of medication.
- They not only boost the stability of the entrapped medication but are also stable and osmotically active.
- Surfactants don't require any specific handling or storage conditions.
- Enhanced epidermal penetration and increased oral bioavailability of poorly absorbed medications.
- They can be administered topically, parenterally, or orally to reach the site of action.

Methods of preparation of niosomes

- Ether injection method
- Lipid film hydration (Hand shaking method)
- Microfludisation
- Reverse phase evaporation
- Ethanol injection method
- Multiple membrane extrusion method
- Sonication Method.[26]

Characterization of niosomes

- Entrapment efficiency
- Optical Microscopy
- Measurement of Angle of repose
- Measurement of vesicle size
- Osmotic shock
- Zeta potential analysis
- Scanning electron microscopy
- Stability studies
- In-vitro methods for niosomes

4.11 Microsponge based gel

A new and innovative method for regulating release and delivering drugs to specific targets is the microsponge. Microsponges, which are mostly utilized for extended topical administration, are polymeric delivery methods made of porous microspheres. The purpose of microsponges is to administer a pharmaceutically active component effectively at the lowest possible dosage, as well as to improve stability, lessen adverse effects, and alter medication release profiles. Due to its many advantageous qualities, microsponge technology provides a flexible method of medication administration. The foundation of Microsponge Systems is a small polymer-based microsphere that may be used to suspend or entrap a broad range of compounds. These microspheres can then be added to a product's formulation, such as a gel, cream, liquid, or powder. Although the microsponge technology can be used in many other formulations, gels are the most common form in which it is produced. Microsponges deliver the active ingredient gradually into the skin after application. Microsponge, which can store four times their weight in skin secretions, do not penetrate through skin.[27-30]

Polymeric delivery systems known as microsponges are made of porous microspheres that have the capacity to hold a broad variety of active substances, including sunscreens, emollients, perfumes, essential oils, and anti-infective, anti-fungal, and anti-inflammatory compounds. A typical 25µm sphere can contain up to 250000 pores and an internal pore structure similar to 10 feet in length. This results in a total pore volume of roughly 1ml/g for substantial drug retention. The microsponges range in size from 5 to 300µm in diameter.

A feature of medication delivery systems using microsponges

- Microsponges exhibit satisfactory stability in the pH range of 1 to 11 and at temperatures as high as 130°C.
- Microsponges show good compatibility with different types of substances and vehicles.
- Microsponges exhibit a high trapping effectiveness of approximately 50–60%.
- Microsponges possess features that allow for unrestricted flow.
- Because the average pore size of microsponges is small (0.25 µm), they do not require sterilization or the addition of preservatives to prevent bacterial penetration.
- Microsponges are non-toxic, non-allergenic, non-irritating, and non-mutagenic.
- Without drying out, microsponges can absorb up to six times their weight in oil.[29,30]

Advantages

- Oil can be absorbed by microsponges up to six times their weight without drying up.
- Extended availability.
- Enhanced product sophistication.
- Improved patient compliance is a result of reduced discomfort and increased tolerance.
- Have improved chemical, physical, and thermal stability.
- It is non-toxic, non-mutagenic, non-irritating, and it permits the addition of immiscible goods.
- Increased adaptability in formulation.
- Easy to use and economical.
- Microsponges are tiny spheres that may absorb skin secretions, which reduces shine and oiliness on the skin.
- Microsponge formulations are self-sterilizing because germs cannot pass through their average pore size of 0.25µm.[31]

Method of preparation of microsponge

- Quasi-emulsion solvent diffusion
- Liquid-liquid suspension polymerization

Evaluation of microsponge

- Dissolution tests
- Determination of loading efficiency and production yield
- Morphology and surface topography of microsponges
- Characterization of pore structure
- Particle size determination
- Determination of true density
- Resiliency (Viscoelastic properties).[27,30,31]

4.12 Gel by qbd

The following components are taken into account when developing a technique for formulating gels:

- QTPP stands for quality target product profile.

- The product blueprint and comprehension, along with the identification of CMA (Critical Material Attributes) of excipients and drug substance, are Critical Quality Attributes of the drug substance, drug product, and excipients.
- Process design and consideration, such as determining a medication product's in-process material properties and CPPs (Critical Process Parameters).
- A control plan and rationale to guarantee the dependability of the product.[41-43]

Target design implementation

When developing new Gel products and processes, the following factors are taken into account:

- The QTPP explains how to utilize gel and its safety and effectiveness.
- During the development of gel formulations, defining QTPP will serve as a quantitative proxy for factors related to chemical safety and efficacy.
- To compile pertinent information regarding the drug's ingredient, excipients, and manufacturing process into a knowledge base.
- Utilizing risk assessment to guide additional research.
- To fulfill QTPP, a gel formulation's CMA (Critical Material Attributes) must be limited when designing the formulation.
- Creating a formulation procedure to produce a final product with the aforementioned CMA.
- To achieve the CMA of the final product, it is necessary to identify the CPP (Critical Process Parameters) and regulate the qualities of the input raw materials.

Qbd approach for gel formulation

Outline of product development:

- Establishing a Target Quality Product Profile.
- Determining the Critical Quality Attributes (CQAs) for the drug product, excipients, and drug substance.
- Identifying and ranking possible hazards for every unit's operation (risk assessment)
- Both screening and formulation optimization are involved.
- Creation of a sturdy production procedure.
- The formulation of control measures.
- Specifications for raw materials

- Process management and oversight, including designing areas for specific or multiple unit operations.
- Specifications for the final product.[42-43]

5. CONCLUSION

Topical and transdermal drug delivery has long been the focus of research on gels. Recent advances in pharmaceutical science and technology have not only enhanced conventional gels, such as hydrogels, as drug delivery systems, but have also brought new semisolid vehicle variations, such as proniosomes and microemulsion gels (MBGs), specifically for transdermal delivery. Although the medicine is effectively delivered through the skin by these new gel technology advancements, there are still numerous issues that need to be resolved. Additional understanding of bigels and aerogels could result in novel discoveries about practical topical and transdermal medication administration. In order to overcome the shortcomings of each gel system and create a cost-effective delivery method for pharmaceutical and cosmetic applications, more research into gel technologies will be helpful.

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