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Nanoemulgel: A Comprehensive Review for Topical Drug Delivery



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Valarmathy S*, Dr. Devi Damayanthi R, Dr. Daisy Chella Kumari S, Surya S, Sri Vidhya P, Vaishnavi Durga G K

Department of Pharmaceutics, College of Pharmacy, Madras Medical College, India.

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ABSTRACT

Nanoemulgel is a highly effective delivery system for lipophilic medications. Nanoemulgel is the term for an emulsion that has gelled with the help of a gelling agent. They can be made in o/w or w/o varieties in which one immiscible liquid is distributed within another liquid as droplets. Hydrogel-based nanoemulsion systems, or nanoemulgels, are homogeneously dispersed systems in which the hydrogel matrix increases the skin penetration of the nanoemulsion (droplet size 10-200 nm). With high drug loading owing to increased solubilizing efficacy, improved bioavailability owing to superior permeability, and the ability to control drug release, it's a powerful alternative delivery technique for treating a variety of ailments. It has been shown that using nanoemulgel formulation to treat inflammation caused by rheumatoid arthritis, psoriasis, fungal infections, acne, and pimples is far more successful. In the future, nanoemulgel is likely to be the mainstay for the topical administration of lipophilic drugs. The application of nanoemulgels modifies the structure of the skin, increasing the drug's permeability through the skin. High water content, bio adhesive properties, high biocompatibility, biodegradability, and the ability to form deposits that allow medications to slowly elute into surrounding tissues while maintaining a high local concentration for an extended amount of time characterize nanoemulgels. A viable method for topically administering a hydrophobic medication is the use of nanoemulgels. This succinct review focuses on nanoemulgel as a more effective topical drug delivery technology, covering its component screening, formulation technique, and recent advancements in pharmacokinetic and pharmacodynamic research conducted by scientists worldwide.



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INTRODUCTION

Nanoemulgel is being an effective delivery system for lipophilic drugs. It enhances the therapeutic profile of lipophilic drugs. Lipophilic drugs show poor solubility, and unpredictable absorption that alter the pharmacokinetics of drugs. Some methods like physical and chemical modifications of API with formulation criteria like particle size reduction, are used to increase the solubility of active moieties.^[1,2,3] New methods are needed to increase topical therapy's usefulness and efficacy. Because decreasing to the nanoscale allows for higher skin penetration, drug delivery techniques using optically transparent nanoemulsions with globule diameters of 100 nm and 500 nm have attracted the attention of researchers.

A gelling agent that promotes transcutaneous administration is added to the nanoemulsion to increase its viscosity and produce a nanoemulgel.

Adhesiveness and film formation facilitate drug penetration because of the hydrating and occlusive properties of the nanoscale.^[4,5]

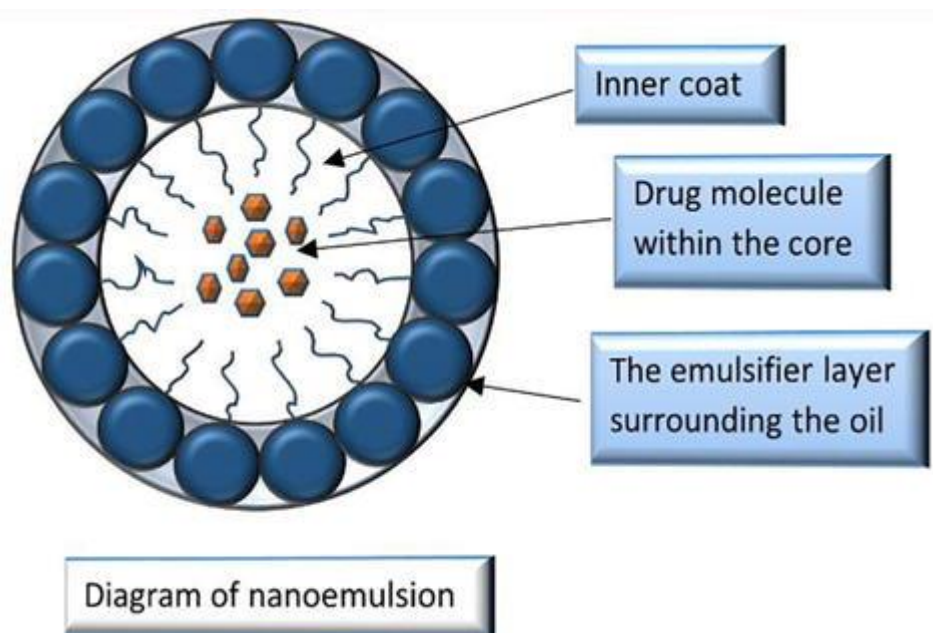


Fig 1: Schematic diagram of Nanoemulsion

SCOPE OF NANOEMULGEL

Nanoemulgel plays an important role in the topical drug delivery system. Topical nanoemulsion gel is a better option than conventional lipophilic drug formulations due to its improved pharmacokinetic profile, higher therapeutic effectiveness, and stronger absorption capacities.

The nanoemulgel formulation's improved spreading properties and reduced stickiness make it a popular choice among patients when compared to other topical administration options.^[6,7] Patient compliance is due to non-greasy qualities and the lack of oily foundation leads to greater medication release when compared to other formulations. Increased spreadability and the resolution of issues related to creaming and phase separation associated with conventional emulsions are achieved with the introduction of Nanoemulsion into the gel matrix. There are topical circumstances where a gel filled with nanoemulsion is more advantageous.^[8,9] Many medications used to treat skin infections have hydrophobic properties. These medications can be effectively administered as nanoemulgels, in which the medicine is incorporated into the oil phase of the nanoemulsion before merging with the gel base.^[10]

ADVANTAGES OF NANOEMULGEL ^[11]

- The drug's affinity for oil dictates stability, and the distribution of oil droplets in the gel foundation enhances the stability of the nanoemulsion.
- Compared to previous topical formulations that have been explored, the nanoemulgel has several advantages, such as the preference to avoid first-pass metabolism.
- Incorporation of Lipophilic drugs.
- Better skin permeability and drug disposition.
- The drug release is controlled by the nanoemulgel.
- Patients always prefer the topical use of nanoemulgel, which improves patient compliance.
- Patients of all ages can accept topical treatment, which is always preferred over oral and parenteral drug delivery.

- The nanoemulgels can be stopped or cleaned off at any moment in the event of any negative effects or localized skin irritation.
- Additionally, a strong concentration gradient caused by good skin adherence with high solubilizing strength increases medication penetration as it descends.

DISADVANTAGES OF NANOEMULGEL ^[12]

- Certain drugs don't absorb well through the skin.
- For those who have contact dermatitis, the medication and/or excipients may cause skin irritation.
- Drugs with larger particle sizes are more difficult to absorb through the skin.
- The potential for allergic responses.

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG:-^[31]

A. Physiological factors ^[33]

- i. Lipid content of the skin - acts as a barrier for drug absorption and lowering this barrier property leads to increased penetration.
- ii. Thickness of different skin layers -Greater the thickness lower the penetration rate, like palm and sole shows a higher diffusion rate compare to other surfaces.
- iii. Hair follicles density - large storage, about 10-12 times than SC.
- iv. Skin pH.
- v. Hydration of skin.
- vi. Sweat gland density.
- vii. Inflammation of skin-disrupted stratum corneum has higher permeability.
- viii. Blood flow.
- ix. Skin temperature

B. Physicochemical factors ^[32]

- i. Partition coefficient - higher log p value gives rise to absorption.
- ii. Effect of vehicles - hydro alcoholic gel provides the most efficient absorption through skin.
- iii. Degree of ionisation.
- iv. Molecular Weight. (Less than 400 Dalton).

FORMULATIVE COMPONENTS OF NANOEMULGEL

1. Oil phase

When choosing oil or other lipid components, care must be taken to ensure that the oily phase is real and shielded from impurities like peroxides, free radicals, and other fatty acids like sterols and polymers.

One of the primary factors in the choosing of lipids for the creation of nano emulates is the bulk of hydrocarbon chains; the rationale for this is the uniformity and essence of emulsification. Mineral oil as a drug vehicle, cottonseed oil, maize oil, Arachis oil, olive oil, coconut oil, eucalyptus oil, rose oil, clove oil, etc. are among the oils that are frequently employed in nanoemulsions.

2. Aqueous phase ^[16]

This component is in charge of turning the emulsion into an emulgel in this instance of the gelling agent.

Generally, distilled or ultra-purified water is used to create the nanoemulgel's composition.

3. Surfactant ^[13]

Surfactants are utilized in the production of nanoemulgel to give the final formulation stability and emulsification. Non-ionic surfactants are employed in the creation of nanoemulgel due to their low toxicity. Among the nonionic surfactants that are frequently utilized are the esters of sorbitan and polyoxyethylene fatty acids.

4. Co-surfactant ^[14]

Co-surfactants are typically employed to increase the final product's thermodynamic stability while reducing the concentration of surfactant. Ethyl alcohol, PG's, Transcutol HP, and PEGs are a few examples of co-surfactants.

5. Penetration enhancers:

One of the finest methods to improve transportation efficiency through the skin and related layers has been to use penetration enhancers. One of the main components of the traditional drug delivery system is penetration enhancer, which is typically utilized in topical nanoemulgel. Usually, these penetration enhancers function by interacting with the constituents of skin, resulting in a transient and cumulative rise in skin permeability.

6. Gelling agent ^[15]

One of the key components of nanoemulgel, the gelling agent, gives the formulation a flawless structure.

These make sense as cross-linking agents. Tragacanth, HPMC, Carbopol, etc. are a few of the gelling agents that are employed.

7. Preservatives:

Preservatives are chemical substances used to protect a substance from microbiological degradation and extend a product's shelf life. Preservatives including methylparaben, Propyl paraben, Benzalkonium chloride, and phenoxyethanol are frequently utilized.

8. Antioxidant:

Antioxidants are chemical compounds used in compositions to prevent various components from oxidizing.

For example, Ascorbyl palmitate, Butylated hydroxytoluene, etc.

9. pH modifiers:

The pH value also indicated the stability of the nanoemulsion. The mean value of pH should lies in the range of 5.4 - 5.9 (pH of skin). Most commonly used pH modifier is Triethanolamine.

Table 1: Formulation of Nanoemulgel

COMPONENT	EXAMPLE
Oil	Castor oil., ethyl oleate., sesame oil., Arachis oil., lanolinCapryol 90., isopropyl myristate., olive oil., oleic acid., isopropyl palmitate., corn oil.
Surfactants (surface active agents)	Nonionic - Fatty alcohols, Glycerol esters, Fatty acid esters. Anionic contain - Carboxylate groups., Soaps., Sulfonates., Divalent ions Cationic- Amines and quaternary ammonium compounds. Zwitterionic surfactants-phospholipids
Co-surfactant	Propylene glycol., glycerine., Lecithin., Propanolol., Transcutol P., Ethanol., Polyethylene glycol Butanol
Gelling Agent	Collagen., Agar., Tragacanth., Guar gum., Gelatin., HPMC., Carbopol934.,940.,941
Penetration enhancer	Alcohols., Polyols., Alkanes., Ester., Terpenes., Surface active agent

METHODS OF PREPARATION OF NANOEMULGEL [17]

I. SCREENING OF COMPONENTS [18]

Based on the findings of the preformulation tests, the formulation's final composition should be carefully chosen. The oily phase is chosen in this step according to how well it dissolves the drug moiety. Based on the characteristic parameters utilized to create the nano-sized emulsion, their compatibility with the oil, and the kind of emulsion (o/w or w/o), the ratios for the surfactant and cosurfactant are chosen. Plotting a pseudoternary phase diagram is one method used to critically examine if the concentration of these components can produce a nanoemulsion. The ratio of these three elements, which serves as the nano emulsification region's stable nanoemulsion development point, is shown by this phase diagram.

II. PREPARATION OF NANOEMULSION

The medication, cosurfactant, and surfactant are dissolved according to how soluble they are in the selected aqueous or oil phase. The aqueous and oil phases are heated independently, and after they reach room temperature, they are mixed by progressively introducing one into the other while stirring continuously.^[19]

Both low- and high-energy techniques can be used to formulate the nanoemulsion. Self-nano emulsification, phase inversion (phase inversion temperature (PIT), phase inversion composition (PIC), emulsification, and solvent diffusion technique are examples of low-energy techniques; ultrasonication, microfluidization, and high-pressure homogenization are examples of high-energy techniques. It is recommended to employ low-energy techniques instead of high-energy ones due to their greater effectiveness and lack of need for sophisticated equipment.^[20]

By using high-energy techniques, the particle size can be adjusted and controlled using different formulation compositions. With high-energy methods, the emulsion's stability, rheology, and color can also be managed.^[21]

High mechanical energy is used to produce strong disruptive forces that break up large droplets into nano-sized droplets and produce high-kinetic-energy nanoemulsions.

The high-energy method reduces the size of both phases by creating an extremely disruptive force with mechanical instruments. Thus, this method might cause the formulation's constituent parts to overheat, which would cause the emulsion to become thermodynamically unstable and render it inappropriate for medications that are thermolabile.

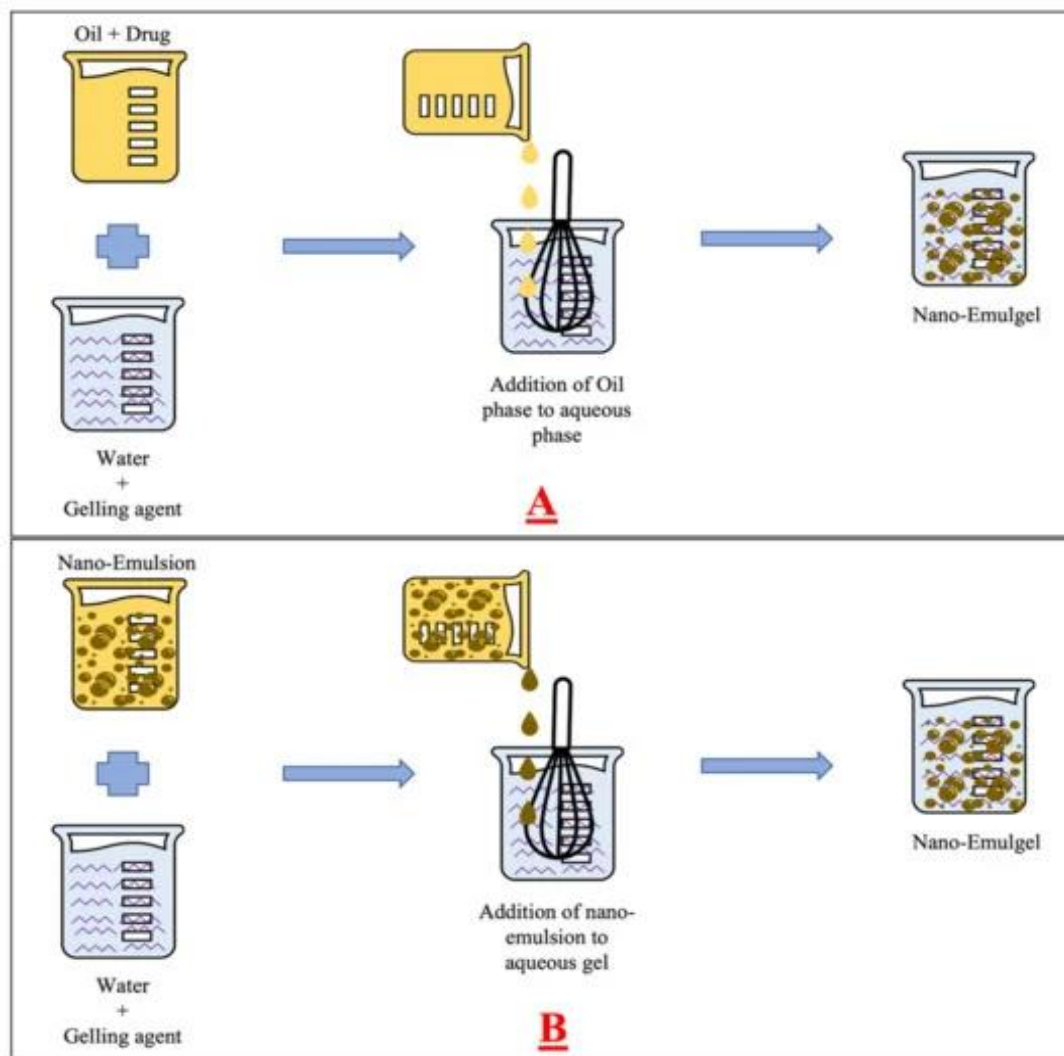
Using the system's inherent chemical energy to increase energy efficiency is a characteristic of low-energy emulsification techniques. Because this method uses less energy, heat-labile components are not degraded. In order to create essential oil-based nanoemulsions and prevent the volatile compounds in essential oils from evaporating, the low-energy or spontaneous technique is widely employed.^[22]

III. PREPARATION OF NANOEMULGEL^[23]

The preparation of gelling media involves dissolving gelling agents into an aqueous medium until complete swelling is achieved. For this, the selected polymer is dispersed in pure water

while being continuously stirred by mechanical means at specified conditions for a specific time and a constant rate to achieve complete swelling. Lastly, the gel base is adjusted for pH, which can be delivered effectively to the topical system.

An o/w nanoemulsion solution thickens to produce gel when a gelling component is added. This is because the agent's thixotropic properties help the formulation transition from a gel to a solution when shear force is applied, without changing its volume. Any of the aforementioned processes can be used to create the nanoemulsion, which can then be converted into an NEG by using a gel base. To incorporate a nanoemulsion into the gel matrix, the gel and nanoemulsion at a fixed ratio are gradually mixed and continuously stirred to maintain homogeneity.



Schematic representation for the preparation of nano-emulgel by (A) adding Oil (oil + drug) phase to the aqueous (water + gelling agent) phase (B) adding nano-emulsion to aqueous (water + gelling agent) phase.

1. High-pressure homogenization method ^[25]

With this technique, the oil phase is broken down into nanosized droplets that are easily dispersed in a hydrophilic gel matrix using a high-pressure homogenizer. High shear forces produced by the homogenization process aid in reducing droplet size and producing a stable nanoemulgel.

2. Ultrasonication method

This process makes Nanoemul gel using ultrasonic waves. After the hydrophilic matrix and oil phase are combined, high-frequency ultrasonic waves are applied to the mixture.

The oil phase is broken down into nanosized droplets by the ultrasonic energy, and these droplets are evenly distributed throughout the gel matrix.

3. Solvent evaporation method

This approach requires the use of a water-miscible solvent to dissolve the oil phase and the hydrophilic matrix. The solvent is then evaporated under decreased pressure, leaving behind a Nanoemulgel with nanosized droplets of oil scattered throughout the gel matrix.

4. Microfluidization method ^[24]

This approach creates Nanoemulgel by passing the oil phase and the hydrophilic matrix through a microfluidizer that produces high shear pressures that break down the oil phase into nanosized droplets that are disseminated in the gel matrix.

5. Self-emulsifying gel method ^[26]

This method involves the use of a self-emulsifying drug delivery system (SEDDS) that can create Nanoemul gel in situ. The SEDDS is a mixture of oil, surfactants, and co-solvents that can spontaneously emulsify when in contact with water. When the SEDDS is mixed with a hydrophilic gel matrix, a Nanoemul gel is formed.

6. High-energy emulsification method

To produce tiny droplets of the dispersed phase (oil) in the continuous phase (water), this method uses a high-energy input. Numerous techniques, including sonication, high-pressure homogenization, and microfluidization, can be used to accomplish this. A gelling agent, such as a polymer or a surfactant, can then be added to the resultant emulsion to turn it into a gel.

7. Phase inversion temperature (PIT) method

This process makes use of a thermosensitive surfactant, which, at a given temperature, phases out of a water-soluble state and becomes an insoluble one. The dispersed phase can be trapped by the surfactant by changing the system's temperature, which causes the surfactant to form a gel-like structure.

8. Sol-gel transition method

This process takes advantage of a sol-gel transition system, in which a network of particles or polymers aggregates in a solvent to produce a gel. This can be accomplished by mixing in a thermosensitive polymer or crosslinking agent to cause the emulsion to form a gel-like structure at a specific temperature or under specific circumstances.

9. Electrostatic complexation method

Through the application of oppositely charged polymers or surfactants, a stable emulsion is produced that can subsequently be gelled or crosslinked.

10. Coacervation method

This process uses two or more polymers that phase separately in the presence of an electrolyte or when the pH changes, forming a structure that resembles gel. The dispersed phase can then be mixed with the gel using techniques like high-energy emulsification.

CHARACTERIZATION OF NANOEMULGEL ^[27]

1. Drug content determination

By diluting the necessary amount of the prepared formulation with phosphate-buffered saline (PBS) 7.4, the amount of drug contained in the prepared nanoemulgel was ascertained. Using PBS 7.4 as a blank, this mixture was examined using a UV spectrophotometer set to 240 nm.

2. pH determination

Since the formulation was intended to be applied topically to the skin, a pH measurement was necessary to confirm that the substance would not irritate the skin. Using a digital pH meter, the formulation's pH was measured at room temperature.

3. Spreadability

As Mutimer suggests, it can be quantified using the Slip and Drag basis. Here, two grams of Nanoemulgel are placed on a lower ground slide that is fastened with a wooden block, and another glass slide of a comparable size is made and fastened with a hook that holds a 500 mg weight. After five minutes, the pan attached to the second slide was given more weight. The time required to cross a 5 cm distance on the upper slide was recorded, and spreadability was computed using the equation that follows:

$$\text{Spreadability (S)} = M * L / T$$

where L = Glass slide length and M = weight attached to top slide

T = Distance traveled in a single slide by upper slide

4. Droplet size, polydispersity, and Zeta potential of Nanoemulsions ^[28]

Dynamic light scattering (DLS) otherwise called photon correlation spectroscopy (PCS) is used to analyze the fluctuations in the intensity of scattering by droplets/particles due to Brownian motion. Nanoemulsions droplet size, zeta potential and polydispersity can be assessed by PCS using a particle size analyzer.

5. Swelling index

1 gm of prepared topical nanoemulgel is taken on porous aluminum foil which is then placed on 10 ml of 0.1 N NaOH solutions. Sample removed from time to time and weight is noted till no further change in weight:

$$\text{Swelling Index (SW) \%} = [(W_t - W_o) / W_o] * 100$$

Where, (SW) % = Percentage swelling,

W_o = Original weight of nanoemulgel

W_t = Weight of swollen nanoemulgel at time t .

6. Viscosity measurements and rheological behavior ^[29]

A Brookfield L was connected to a thermostatic water bath adjusted to 25°C. Viscosity was measured on each base by using spindle 40. A defined amount (1 g) of each gel base was placed inside the plate and carefully closed. The measurement was started by operating the viscometer at 0.6 rpm, the speed was gradually increased and the measurement was recorded when the torque reached 10% was obtained by plotting the shear rate as a function of the shear stress.

7. Skin irritation test

0.25 gm Nanoemulgel is applied to each different site (two sites/rabbit). After 24 hr of application rabbit skin sites are wiped and cleaned, Change in color of skin or undesirable change in morphology is noted and checked.

8. Invitro diffusion studies

Franz diffusion cell is used to perform diffusion study of prepared nanoemulgel. A cellophane membrane is used for study and 0.5g of sample is applied on the membrane and diffusion is carried out for 8 hr at 37±1°C using phosphate buffer (pH 7.4). At a time interval of 1 hr, 1 ml pg sample is collected and replaced with a new buffer solution. Collected samples are analyzed by using a suitable analytical method.

9. Ex vivo drug permeation studies ^[30]

Franz diffusion cell was used in the ex vivo permeation investigations because it is a dependable technique for estimating drug transport through the skin. These investigations were carried out using Wistar rat's removed skin. Using surgical blade No. 24, the hair on the dorsal side of the sacrificed animal was cut in the direction of the head towards the tail. Using a knife, the shaven portion of the animal's skin was split, and extra fat and connective tissue were cut out. After being removed, the skin was cleaned using regular saline, checked for integrity, and then used. The diffusion cell's receptor compartment was filled with 20 milliliters of pH 7.4 phosphate buffer. During the experiment, the temperature was kept at 37 ± 0.50°C and the assembly was mounted on a magnetic stirrer. Magnetic beads were used to continually mix the solution in the receptor compartment at 100 rpm. The skin was placed

atop a diffusion cell assembly that had a 4.91 cm² effective diffusion area (orifice area). One gram of the produced formulation was applied to the donor compartment membrane. At appropriate intervals, a 2 mL sample aliquot was taken out and quickly replaced with an equivalent volume of brand-new diffusion medium. The samples underwent spectrophotometric analysis. Plotting the drug permeation per cm² of membrane versus time allowed for the calculation of flux, which was determined as drug permeation per cm²/h.

10. Comparison of permeation studies with marketed formulation

Formulation, optimized nanoemulgel, nanoemulsion, plain drug gel and drug solution. The ex vivo permeation study of the optimized nanoemulgel formulation was compared with the marketed formulation for permeation and retention characteristics. The cumulative amount of drug permeated through the skin per unit area was plotted as a function of time. The permeation rate of drug at steady state (J_{ss} mg/cm/h) through the skin was calculated from the slope of the linear portion of the plotted curve. The lag time (T_{lag}) was determined by extrapolating the linear portion of the cumulative amount permeated versus the time curve to the abscissa. Enhancement ratio (E_{pen}) was calculated by dividing J_{ss} of the respective formulation with J_{ss} of control formulation.

11. Release kinetics

To study the release kinetics, data obtained from ex vivo permeation studies were fitted in various kinetic models:

- Zero order as a cumulative percent of drug released versus time,
- First order as log cumulative percentage of drug remaining versus time.
- Higuchi's model as cumulative percent drug released versus square root of time.
- To determine the mechanism of drug release, the data were fitted into the Korsmeyer and Peppas equation as log cumulative percentage of drug released versus log time and the exponent n was calculated from the slope of the straight line.
- For the slab matrix, if the exponent is 0.5, then the diffusion mechanism is fickian; if $0.5 < n < 1.0$, the mechanism is non-fickian.

12. Accelerated Stability studies

As given in ICH guidelines, the formulations are stored in the oven at $37\pm 2^{\circ}\text{C}$, $45\pm 2^{\circ}\text{C}$ and $60\pm 2^{\circ}\text{C}$ differently for 3 months. Drug content is analyzed every two weeks by a suitable analytical method. Stability measurement is based on changes in pH of gel or drug degradation.

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