Nanoemulgels: A Promising Drug Delivery System for Enhanced Therapeutic Efficacy

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Abstract— The lipophilic nature of many newly developed drugs often leads to poor bioavailability and variability in pharmacokinetics, necessitating the development of novel delivery systems. Among these, nanoemulgel, a transdermal delivery system, has shown promise in improving the systemic delivery and therapeutic profile of lipophilic drugs. This formulation outperforms conventional oral and topical drug delivery methods by minimizing disturbances and enhancing drug stability, bioavailability, and therapeutic efficacy.

Nanoemulgel combine nanoemulsions, which contain the drug, with a gel base, creating a non-greasy, highly viscous, and stable formulation. The finely distributed oil droplets within the gel significantly enhance the skin permeability of the incorporated drug, making it an effective topical delivery system. This method targets the drug to peripheral sites of action, bypassing first-pass metabolism and overcoming gastric system incompatibilities.

This review evaluates the potential and future prospects of nanoemulgel formulations as effective delivery systems for poorly water-soluble drugs. It covers methods of preparation, component screening, formulation strategies, and recent advancements in pharmacokinetic and pharmacodynamics properties, as evidenced by global research studies. The findings indicate that nanoemulgels represent a significant advancement in drug delivery technology, particularly for enhancing the systemic delivery and therapeutic profile of lipophilic drug.

Keyword - Nanoemulgel; Nanoemulsion; Topical drug delivery; Pharmacokinetics; Pharmacodynamics

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I. INTRODUCTION

Since the beginning of pharmaceutical culture in Mesopotamia (2600 B.C.), pharmacists have been able to build the age of current dosing methods through the use of water and plants for medicinal purposes [1]. To administer the created contemporary dosage forms, researchers in this discipline have produced a number of delivery methods. The physicochemical properties of the active ingredient mostly determine the dose forms. The creation of lipophilic active pharmacological substances is a result of a recent trend in synthetic drug development or high throughput screening. [2]. The first finding of around 40% of novel chemical entities (NCE) having poor solubility has been surpassed by recent statistical data on poor aqueous solubility (70%) [3]. The recently discovered therapeutic compounds' lipophilic properties can cause issues such as inconsistent absorption, lack of dosage proportionality, intra- and inter-subject pharmacokinetic variability, and low oral bioavailability.

The formulation strategy is a constantly evolving process that aims to address such problems and concentrate on improving solubility. To increase the solubility of medications that are poorly soluble, a variety of techniques can be employed, including formulation creation, chemical modification, and physical modification (Figure 1). Many formulation strategies, including particle size reduction to distribute via nanocarriers systems, crystal engineering, amorphous formulation [1-5], multiple lipid formulation strategies, etc., have been used to increase the solubility of weakly water-soluble medicines. To address these issues with the lipophilic properties of compounds, newer lipid formulation techniques—such as the incorporation of a lipophilic component in an inert lipid vehicle, the creation of microemulsions or nanoemulsions, self-emulsifying formulations, liposomes, solid lipid nanoparticles, or lipid nanocarriers [6]—are gaining traction. As a result, a number of delivery methods have been investigated to administer those formulations, taking into account their unique benefits and drawbacks with regard to the target site, illness severity, patient age and condition, available dose form, and user compliance.

Oral administration is the most recommended method when it comes to patient compliance; nevertheless, it is more likely to cause hepatic first pass metabolism, which necessitates a greater dose [1-4]. Further, gastrointestinal irritation is the key limits for the inclusion of surfactants in the lipid-based formulations [7-11], simultaneously the distribution of medicine throughout the body can lead to unavoidable adverse effects. Therefore, to avoid such unacceptable issues, a different approach that has several benefits—including delivering the drug to a specific site of action with reduced systemic toxicity, avoiding first pass metabolism and gastric irritation, improving percutaneous absorption by increasing the drug's release rate from the formulation, and occasionally having benefits related to topical application—is the non-invasive, non-painting, and non-irritating topical delivery of the formulation. [1,6,9,14,17].

Traditional transdermal formulations, such as ointments, creams, and lotions, have numerous drawbacks in addition to the previously mentioned benefits. These include their sticky consistency, poor spreadability, stability problems, and other issues that ultimately result in patient noncompliance. Transparent gel and emulgel with increased patient compliance and enhanced efficacy were discovered through the formulation's modernization of transdermal distribution. Thus, these formulations are attracting interest both in cosmetics businesses, as well as in pharmaceutical industries. In spite of many of advantages of gel and emulgel formulations, distribution of hydrophobic medication still remains a huge hurdle to jump over. Furthermore, researchers are extremely concerned about skin penetration through the stratum corneum because to the systemic activity of transdermal administration. [12]

According to published research, topical formulations with nanoscale particles might increase the permeability of the active component by breaking down the lipid bilayer, as demonstrated by the noticeable voids and empty spaces in skin samples treated with nanoemulsions [13] and by retaining the drug longer at the site of action. Being an isotropic, transparent (or translucent) heterogeneous combination of two media (oil and water), with one phase dispersed in the other and stabilized by an interfacial coating of surfactant molecules, nanoemulsions have a lot of hope.

According to studies, nanoemulsions can dissolve drugs more readily than simple micellar solutions. Additionally, because of their thermodynamic stability, they have a longer shelf life and can be produced with less energy input than unstable dispersions like emulsions and suspensions [18]. Even while nanoemulsion has several benefits, its low viscosity and spreadability limit its topical application

By simply converting nanoemulsion to nanoemulgel, researchers have been able to tackle the issues related to nanoemulsion for transdermal distribution. By employing a gelling agent, nanoemulgel can be created from nanoemulsions of the water-in-oil (w/o) or oil-in-water (o/w) type [1,18]. With enhanced nanoemulsion qualities for transdermal application, nanoemulgel has gel characteristics. Comparing nanoemulgel to other carriers such microemulsions, liposomes, or solid lipid nanoparticles, additional benefits include less skin irritation, increased permeability, and high drug-loading capacity for topical delivery [22]. Medicinal chemicals can be added to this colloidal delivery system to boost bioavailability, raise stability plateau, and lessen side effects [25]

Through appropriate percutaneous absorption within the skin to improve local efficacy and/or through the skin to the circulation to polish its systemic effect, nanoemulsion ensures adequate localization and dispersion of the drug. It can even cross the rigid blood-brain barrier to offer additional advantages in CNS activity. [27]

The results of numerous investigations on the permeability, pharmacokinetics, pharmacodynamics, and safety profiles of medications administered using topical nanoemulgel are compiled and discussed in this study. We compare the ex-vivo/in vitro permeability, pharmacokinetics, pharmacodynamics, and safety profiles of this drug delivery system in order to objectively assess its rationality and potential future applications. We also discuss the main obstacles to be addressed in the nanoemulgel formulation process.

When compared to the previously listed dosage forms, nanoemulgel has comparatively greater penetration, stability, and effectiveness. It also has less greasiness and is easier to incorporate hydrophobic medicines into. the majority of innovative medication administration.

Regarding transdermal distribution, BCS class II and/or IV medications may be better suited for a pharmaceutically modified nanoemulsion that includes an appropriate gelling agent. [22]

Drugs can penetrate into the skin structure:

a. through thick stratum corneum, (SC)

b. Sebaceous follicle.

c. sweat ducts of skin,

Over 99% of skin is covered by the stratum corneum, which makes it possible for medications to be absorbed. The rate-limiting stage for medication percutaneous absorption is getting past this. One of the key processes in percutaneous absorption is the establishment of a concentration gradient, which supplies the force required for drug adsorption through the skin. [28]

Skin structure

The average adult human epidermis has 40–70 hair follicles and 200–300 sweat ducts per square centimeter, measuring 1.8 m2 Depending on the secretions from the sweat glands, the pH of the skin can range from 4 to 5.6. There are three layers to the skin:

a. Epidermis

b. Dermis

c. Hypodermis

a. Epidermis

The outermost layer of the skin, known as the epidermis, is made up of stratified squamous epithelium, which is divided into two layers: the superficial stratum, or stratum corneum, and the deeper stratum, or stratum basale. The stratum corneum, the outermost layer of skin, is made up of 10 to 20 layers of cells and hardens as a result of the keratinization process. It serves as a physical barrier to the majority of medications. The flat, plate-like cells of SC measure 2500 µm in width, 34–44 µm in length, and 0.5–0.20 µm in thickness. The lipid composition of SC consists of phospholipids, cholesterol sulfate, glycosphingolipid, a neutral lipid, and keratin, a protein. The stratum basale, which has a thickness of 50–100 µm, is located between the SC and the dermis. This layer's cell structure is comparable to that of other biological tissues. This layer mostly contains about 90% water.

b. Dermis

Deeper and thicker (2000 to 3000µm) region beneath the epidermis is called dermis, mostly contracted with structural fibrin and very few cells same as found in normal tissue. Dermal papillae are outer most layer having signalized projection. It also contains oil-secreting glands, sweat glands, nerve ending and hair follicles. Elastic and collagenous fibers within dermis provide stretch ability and tone to the skin. The density of its fiber meshwork, and therefore its physical properties, varies within an area, in different parts of the body, and with age and sex. [23-26].

c. Hypodermis/Subcutaneous layer

The hypodermis, composed of loose connective tissue varies in thickness, merges with the deep lower part of the dermis. Apart of this it also composed of secretary sweat glands, fibrous tissue containing blood vessels and lymph vessels, and cutaneous nerves. Many consider that drug get absorbed into the systemic circulation without passing through this layer by means of blood vesicles and sweat glands [23]

Penetration of drug through skin

There are two pathways of permeation of drugs through the skin those are as follows

1. Trans follicular

The Trans follicular pathway is also known as the shunt pathway. Its secondary pathways for permeation are the skin's extensions. Oil glands and apocrine glands of the stratum corneum are thought of as a shunt pathway for drug diffusion. The body iscovered in a large number of sebaceous and eccrine glands. Apocrine glands have a lotof microscopic orifices. Because apocrine glands are so vigorous, molecules could permeate inside in opposition to the activity of the glands. The Shunt Pathway (follicular route) is a crucial route for permeation [29].

2.Trans epidermal Absorption

Diffusion of drug molecules over the skin is primarily controlled by the trans epidermalor trans organizational characteristics pathway. The completely developed activity helps that makes up this layer, which is characterized as a "brick wall," is immersed inthe motor produced by the lipid bilayers and serves as the brick. Crosslinked keratin filaments create a matrix inside the corneocytes. The structural resilience of the stratumcorneum is due to keratin filaments. Inside this passage, the stratum corneum is the main obstruction [23].

There are two permeation pathways that make up the trans epidermal pathway.

1.Intracellular route: The mechanism of transportation involves partial segregation into the keratinocytes and absorption via the hydrated keratin.

2.Intercellular route: The tiny, unaltered molecule is transported mostly via the lipid molecules route [31].

Factors Affecting Topical Absorption of Drug

There are two factors that affect the topical absorption of drugs those are as follows.

1) Physiological Factor

- Absorption of substance through skin depends on various factors includeconcentration, physical condition of skin & solubility of medication.
- Drugs that are soluble in both aqueous & lipid phases only would be able to penetratethe skin.
- Drugs with high molecular weight have low penetration (<400 Dalton).

2) Biochemical factors

- Increasing the pH in a solution containing the drug substance applied onto the skindecrease permeability.
- Higher volume of surfactant decrease absorption due to unavailability of drug molecules.
- Only the unionized form of drug can be permeating through lipid layer.

Ideal characteristics of nanoemulgel-

1)The ideal particle size for nanoemulsions is small droplets, usually between 20 and 200 nm, in order to optimize medication delivery and stability.

2) Stability: Phase separation, creaming, or sedimentation over time should not occur in the formulation; it should be physically stable.

3) Viscosity: It should adhere to the site of action and be easily applied with the right viscosity.

4) Bioavailability: Better penetration and absorption are made possible by the droplets' small size, which enhances bioavailability.

5) High drug loading capacity: Able to provide a therapeutic dose in a tiny amount of material.

6) Release Profile: Slow, steady release of the medication to keep therapeutic doses stable for a long time.

7) Biocompatibility: The substance is non-irritating, non-toxic, and compatible with the skin and mucous membranes.

Composition of Nanoemulgel –

Nanoemulgel consist of two different systems: the gelling mechanism and the emulsion with tiny droplets. Emulsions of the water in oil or the oil in water kind are feasible. The emulsions are stabilized during the drug delivery process by an emulsifier. The gels are composed of polymers that expand when a liquid is absorbed. A typical nanoemulgel formulation includes the following essential components:

Oil selection

Lipid, or oil, is one of the main ingredients of the nanoemulgel. According to the formulated nano emulsion's viscosity, permeability, and stability, many investigations are needed to choose the right oil phase. When using certain natural oils' medicinal properties, choosing the right oil phase might also be influenced by this. Plant oils that include long-chain fatty acids have been found to have inadequate emulsification characteristics, leading to unstable nanoemulsions depending on the oil's origin. [42]

However, it was discovered that when the oil had reduced hydrophobic properties, its emulsification properties were better [44]. On the other hand, greater hydrophobicity has an impact on the lipophilic medications' solubility in it. As a result, choosing the right oil is an essential stage in the creation of formulations.

Surfactant and co-surfactant selection

Surfactant

Surfactants are integral component of nanoemulsion system which is used to stabilize the thermodynamically unstable mixture of two immiscible liquids by reducing the interfacial tension between them and change the dispersion entropy. Safety, stability and high drug loading capacity along with good emulsification properties are the basic requirements for the surfactants integrated in nanoemulsion development, [49]. A suitable surfactant used in nanoemulsion formulation should be adsorbed rapidly onto the interface of the two immiscible phases leading to dramatically reduction of interfacial tension and prevents coalescence of the nano droplets [49].

Co-surfactant

Co-surfactant helps surfactant in the nanoemulsion system to emulsify oil in aqueous phase. In such system, co-surfactant combines with surfactant and penetrates into the surfactant layer, thereby disrupts the interfacial film, and confers required fluidity, lower the interfacial tension, and help emulsification process [49]. Usually, transient negative interfacial tension and fluid interfacial film cannot be achieved by using surfactant only, so incorporation of co-surfactant provide flexibility to the interfacial film. Co-surfactants may also help in solubilization of the oil by modification of the curvature of the oil-water interface. Selection of co-surfactant is important because release of therapeutic agent or lipophilic drugs affected by its partitioning in aqueous and oil phase by interaction between surfactant and co surfactant [49].

Preparation of nanoemulsion and change its physical state by addition of gelling agent:

The process of manufacturing nanoemulgel involves two steps: the first stage involves manufacturing the nanoemulsion, and the second step involves introducing the nanoemulsion into the gelling agent (Figure 3). By lowering the interfacial tension at the oil/water interface, compositions can mix spontaneously to form nanoemulsions, or they can be created by adding external energy to a heterogeneous mixture [48-52]. Therefore, using both high-energy and low-energy emulsification techniques, it is possible to prepare a thermodynamically stable nanoemulsion.

Step 1:

High-Energy Emulsification Method

By adjusting the necessary time, temperature, and component properties to minimize the size of the dispersed to the nano-range, high shear force generated by ultrasonicators, high pressure homogenizers, microfluidizers, etc., is used to rupture the oil phase and form nanosized droplets in the aqueous phase [48]. As a result, the processes used to prepare nanoemulsions involve the input of external energy, which causes the formulations that are created to be thermodynamically unstable since they include free energy [1]. Furthermore, by modifying the components, this approach can be used to get the dispersed phase size as low as 1 nm; however, it is not appropriate to components that are thermolabile [1].

Low Energy Emulsification

Technique Since high energy is added during the manufacturing process, low-energy methods for creating nanoemulsions, such as phase inversion and spontaneous methods, are found to be superior to high energy emulsification techniques in terms of the final formulation's thermodynamic stability . A perfect mixture of water, oil, and surfactant could create the nanoemulsion on its own; alternatively, the desired Nano-structured droplets could be distributed throughout the continuous phase by adding an aqueous phase, either with or without surfactant, to the oil phase. The emulsification process is influenced by the basic component addition sequence, medium pH, integrated surfactant qualities, and co-surfactant properties. [51].

In particular, this technique makes use of temperature-dependent changes in HLB for specific non-ionic surfactants, primarily poly-ethoxylated surfactants (e.g., Tween 80, Tween 60, Tween 20, Cremophor EL, Labrasol, etc.). The best way to introduce the thermolabile components into the nanoemulsion is through a spontaneous technique. Alternatively, temperature dependent spontaneous twist of non-ionic surfactants is used for phase transition during phase inversion procedure. As the emulsion cools while being constantly stirred, the phase inversion temperature will cause it to reverse. The incorporation of thermolabile components is another constraint of this technique; however, this limitation may be overcome by achieving a lower phase inversion temperature and choosing the surfactant or surfactants appropriately.

Step 2:

Gelling agents can transform nanoemulsion made using any of the aforementioned techniques into nanoemulgel. The gelling ingredient is added to the nanoemulsion formulation with the intention of changing its physical state from liquid to gel. An o/w nanoemulsion system can be thickened by adding a gelling agent, which creates a gelled-like structure. This is because the agent is thixotropic, which aids in the gel-solution transition when shear force is applied to the formulation without causing a change in volume.

Additionally, the state will automatically reverse from solution to gel upon standing. A number of frequently used gelling agents, such as carbomer 940, chitosan, carbopol 934, carbopol 940, carbopol-980, poloxamer 407 [52], methyl cellulose, carbopol 971, etc., are utilized in the creation of nanoemulsion gel. The pharmacokinetic characteristics of the medication included into this nanocarrier system have been demonstrated to be impacted by the addition of a gelling agent to the nanoemulsion. In order to achieve full swelling, gelling chemicals are dissolved into an aqueous medium while being constantly stirred at a steady rate under particular circumstances for a predetermined amount of time. In order to achieve homogeneity, the emulsion will then be continuously mixed at a specific ratio and added to the created gel. [60-61]

Evaluation of Nanoemulgel-

Physicochemical evaluation of developed nanoemulsion and nanoemulgel-

1.Stability studies of developed formulation

Under stress, the optimized nanoemulsion and nanoemulgel stability experiments were conducted in accordance with the ICH 2016 (International Conference on Harmonization, ICH 2016) guidelines, utilizing the technique with minor modifications [61].

1.1 Heat cooling cycle study

Both the nanoemulsion and nanoemulgel underwent a heat-cooling cycle investigation. Before being brought to room temperature (25 ◦C), the formulations were first kept in an incubator at a temperature of 40 ◦C for four weeks. The aim of this test was to identify any turbidity, separation of any emulsion phase (such as cracking and creaming), and physical appearance changes (such as color and texture [53].

1.2 Freeze thaw cycle

For four weeks, the formulations were subjected to a freeze-thaw cycle at a temperature of 2 ◦C. After being removed from the freezer, both the nanoemulsion and nanoemulgel were warmed to room temperature (25 ◦C). The assessment of the changes in texture and shape in the formulation was conducted at two different temperatures [61,53].

1.3 Centrifugation study

Both the nanoemulgel and the blank nanoemulsion underwent phase separation analysis in accordance with earlier research. The ultra-centrifuge was used to conduct the investigation. In a nutshell, the two formulations were put in an Eppendorf tube and run for 10 minutes at 5000 and 10,000 rpm. [53,61]

2.Globule size, PDI and zeta potential assessment of drug-loaded nanoemulsion

Dynamic light scattering is the most widely used method for determining globule size and size dispersion. It can measure the diameter of scattered globules up to 1 nm. In order to ascertain the globule size, PDI, and zeta potential of the produced formulations, the Malvern ZetaSizer (NanoZS-90, Malvern device, Worcestershire, UK) device was utilized [18]. To lessen the impacts of multiple scattering, all formulations were diluted 50 times with deionized distilled water before to the corresponding measurements. The light scattering was measured at room temperature (25 ± 2°C) at a 90° angle. However, the surface charge of the globules at the same temperature was measured using the same apparatus. [53]

3.Measurement of pH, refractive index and electrical conductivity of the developed formulations

To prevent allergic responses or irritations, topical formulations should be non-irritating and have a skin-pH that is compatible with the skin [22]. To find the pH of the nanoemulsion, a calibrated pH meter (Sartorius PB-10) was utilized. Determining the refractive index (RI) value is crucial as it indicates the formulation's isotropic character and clarifies the chemical interaction between the medicine and the excipients [53].

Filming the appropriate nanoemulsion in triplicate on a slide at 25°C allowed for the determination of the refractive index using AtagoRx-5000refractometer[20].

The o/w type of the matching nanoemulsions was ascertained by passing an electrical current through each formulation. Any departure from the microprocessor-based conductivity [61]

4. Analysis of drug content

The drug content assessment was performed according to the approach of Burki et al, slightly modified. For this purpose, around 5 mL sample of drug equivalent to 50 mg of medication was obtained and placed into 100 mL volumetric flask. The mobile phase (ortho phosphoric acid solution: methanol) (25:75) was then added in 35 mL and sonicated for 10 minutes to dissolve it. The sample was allowed to cool at 25 ◦C and made up the volume up to 100 mL with mobile phase. After that, the material was centrifuged for five minutes at 5000 rpm in a Scilogex centrifuge (USA). Using mobile phase, the sample was diluted to 50 mL. The sample was run through a filter with a 0.45 µm pore size nylon filter membrane. The acquired [61,62]

5. Viscosity measurement

The viscosity study of the created blank and drug-loaded formulations was assessed at regular intervals (Day 0, Day 7, Day 14, Day 21 and at Day 28) at the prescribed temperatures, i.e., 8 ◦C, 25 ◦C, and 40 ◦C, using a viscometer (NDJ, 8S, Korea). In this process,

the viscometer's fourth spindle was used to test the viscosity. The spindle's rotation was varied between 6 and 12 rpm for a few minutes while data were being taken [50-61].

6.FTIR analysis

Fourier Transform Infrared Spectroscopy (FTIR) was used to analyse the created nanoemulgel, the pure medication, and formulation ingredients (Carbopol 940 powder, Tween 80, and PEG-400). For every sample, it was examined within the wave number range of 4000 to 400 cm− 1. The purpose of the study was to examine how the medication interacted with the different NEG components [61,62]

7.Swelling Index:

On a porous aluminium foil, 1 gm of the produced topical nanoemulgel is applied, and 10 ml of 0.1 N NaOH solutions are poured on top. Sample taken out periodically, and weight is recorded till it stays the same:

Swelling Index (SW) % = [[Wt-Wo]/Wo*100 Where,

(SW) % = Percentage swelling,

Wo = Original weight of nanoemulgel

Wt = Weight of swollen nanoemulgel at time t

8.Spreadability of NEG

With a few slight modifications, Burki et al. (2020) developed the "Drag & Slip" approach, which was used to examine the spreadability of the nanoemulgel, which is an extremely critical factor. This gadget is composed of a wood block with two glass slides—one fixed and the other movable—and a pulley fastened to a single terminal. The two glass slides are the same size; one is moveable, and the other is fixed to the block. To test the mixture's spreadability, a 2 g sample was placed on top of the fix slide and sandwiched between the upper mobile slide and the stationary slide. A 50 g weight was fastened to the pulley's top glass slide. The duration of the upper slide's travel was noted. An analysis was done on the spreadability. [53,61]

S = MxL/T

Where, S = spreadability,

M = weight placed on the movable slide,

L = length of slides,

T= time taken to cover distance

9.In-vitro drug release

The methodology of with several changes was used to carry out the in-vitro drug release investigation of NE and NEG. For this, IPS Technologies, India's Franz diffusion apparatus was employed. Its two compartments, donor and receptor, have capacities of three millilitres and six millilitres, respectively. The temperature was adjusted to 37 ◦C (±1 ◦C) and the stirring speed was 300 rpm prior to loading the samples. In vitro release experiments are conducted using artificial membranes. As a result, the donor and receptor compartments were separated by a cellulose acetate membrane (Sartorius, Germany). The donor chamber was loaded with 2 g of NE and NEG samples, and a pH 5.5 sodium acetate buffer was supplied to the receptor chamber. Using a syringe, a sample (2 mL) was taken from the receptor chamber at the designated intervals. To keep the receptor chambers in the sink condition, fresh buffer was added. Subsequently, the drug's release behaviour was investigated and the samples were evaluated using the UV visible spectrophotometer [53,61,62]

10.Ex vivo and in vivo studies

10.1 Preparation of skin

Using an ex-vivo permeation study with a greatly altered approach, albino rat skin was used. For this reason, an approximately 200-300-gram male rat was removed from the animal housing. Rats were sacrificed by means of cervical dislocation operation. With a surgical blade, the dorsal skin was cut off. The skin was defatted, cleaned, and then wrapped in aluminium foil and stored in the refrigerator for later usage. The Franz diffusion cell equipment was used for ex-vivo permeation on test day, following an hour of soaking in warm water. It was taken out of the refrigerator [61]

10.2 Ex-vivo permeation

A few modifications were made to the way the medication permeated the skin of the rats. Prior to loading the samples, the apparatus's temperature and speed were calibrated to 37±1 ◦C and 300 rpm, respectively. The apparatus's donor and receptor compartments were sealed shut using pre-prepared rat skin. At predetermined intervals—0, 1, 2, 4, 8, 12, 18, and 24 hours—samples were extracted from the receptor chamber using a spinal syringe, and the chamber was then replenished with new buffer solution to maintain the sink condition. A UV-visible spectrophotometer was then used to assess the samples, and data on ex-vivo penetration was noted. [61]

Table 1: List of components

Formulation	Use	Example
Aqueous Phase	For aqueous phase emulsion	Water, alcohol
Oil Phase	For oil phase emulsion	Oleic acid, emu oil
Surfactant	Reducing surface tension	Cationic: hexadecyl trimethyl ammonium bromide, quaternary ammonium compounds, and dodecyl dimethyl ammonium bromide Nonionic: Poloxamer 124, Tween 20, Tween 80, Caproyl 90 Anionic: sodium dodecyl sulfate and sodium bis-20 ethylhexylsulfosuccinate Zwitterionic: carboxybetaine
Co-surfactant	Help improve surfactant performance	PEG-400, Transcutol HP, ethyl alcohol
Gelling Agent	Increasing viscosity	Natural: pectin, carrageenan, alginate acid, xanthan gum, acacia gum Synthetic: carbomer Semi synthethic: hydroxypropyl cellulose, ethyl cellulose
Preservative	Protection from microorganism	Methylparaben, propylparaben, benzalkonium chloride, benzoic acid, sodium benzoate
Antioxidant	Prevent degrading preparation by oxidation	Butyl hydroxy toluene (BHT), Butyl hydroxy anisole (BHA)
Humectant	Maintain moisture	Glycerin, propyleneglycol
Penetration Enhancer	Enhancing drug penetration into skin	Isopropyl myristate, urea, chenopodium oil, pyrrolidone, dimethyl sulfoxide, linoleic acid, menthol

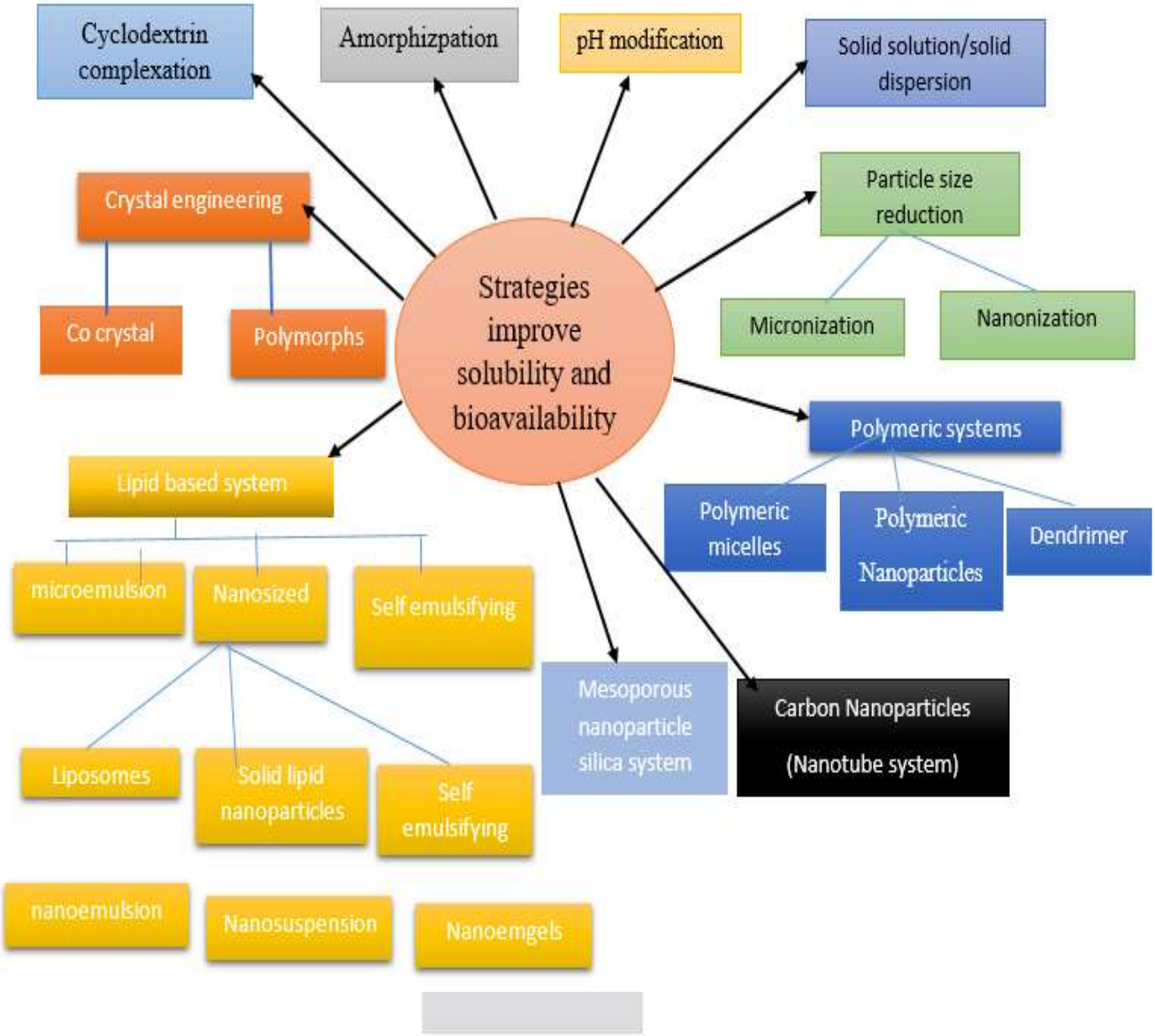

Figure 1: Possible strategies to improve bioavailability of poorly water-soluble drugs [1]

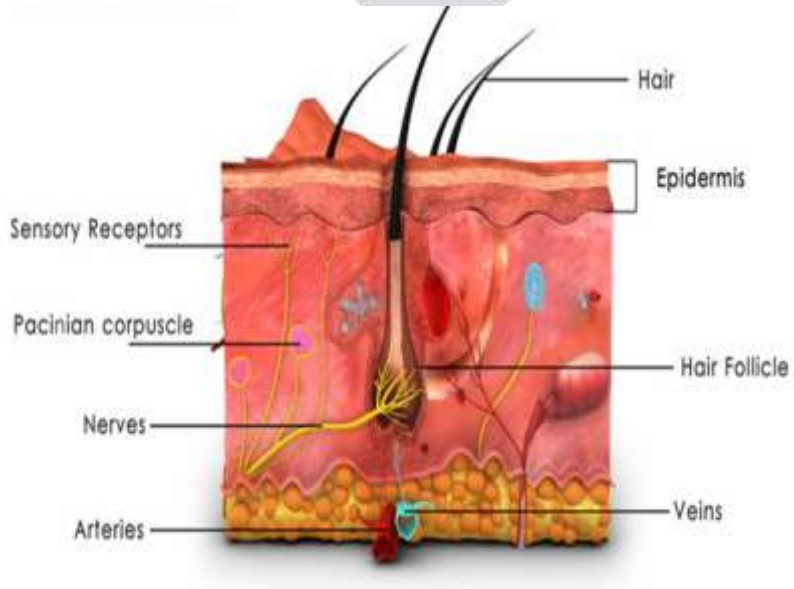

Figure no 2: Structure of skin

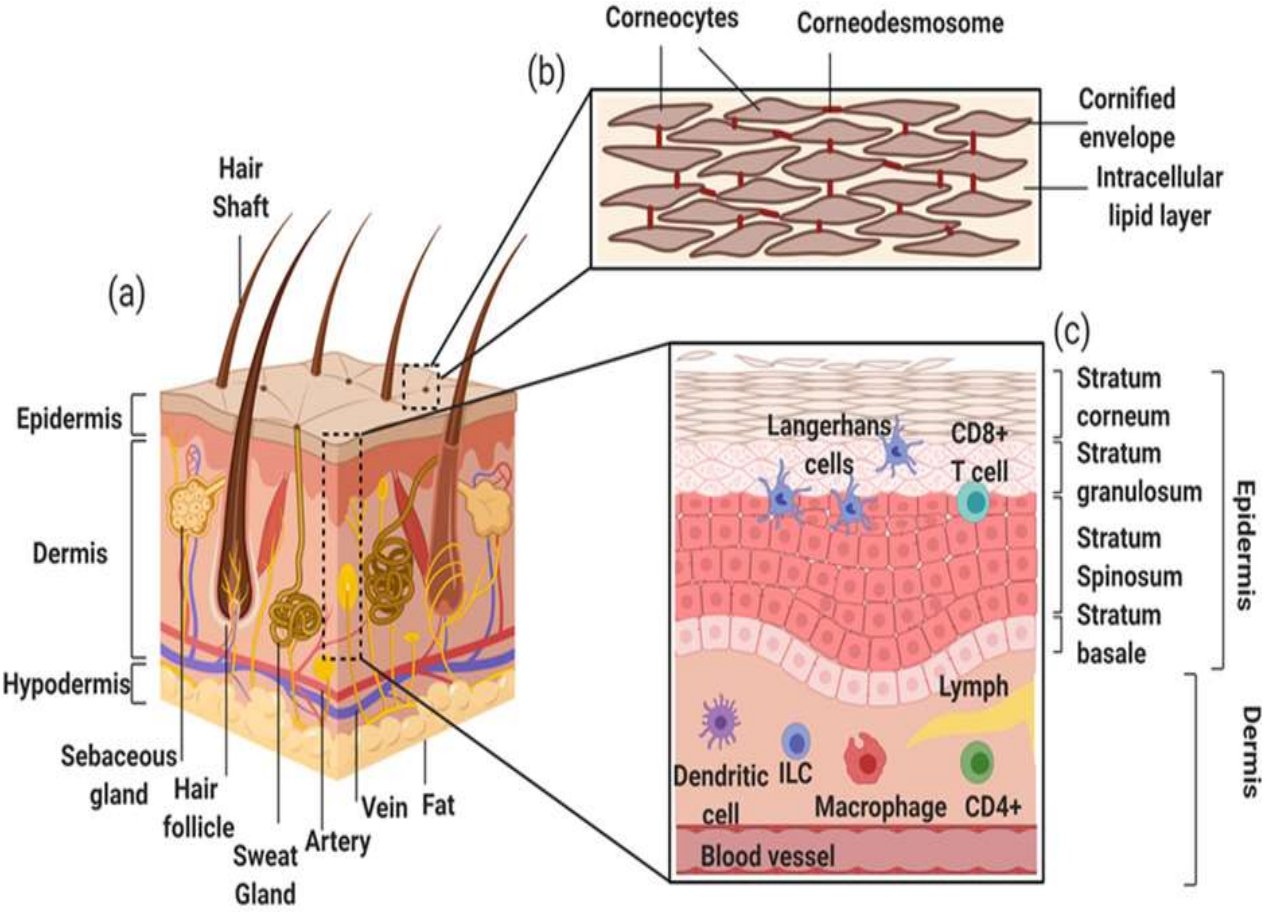

Figure no 3: Different layers of skin

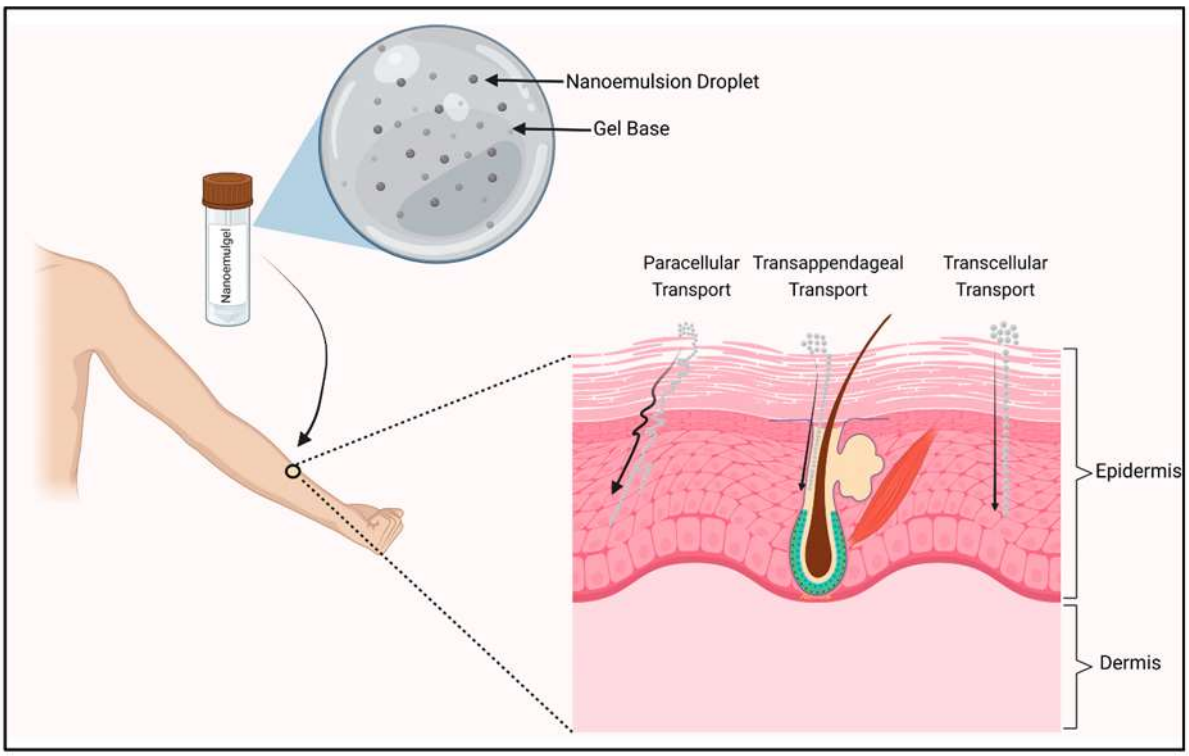

Figure no 4: Mechanistic representation of nanoemulgel delivery via skin

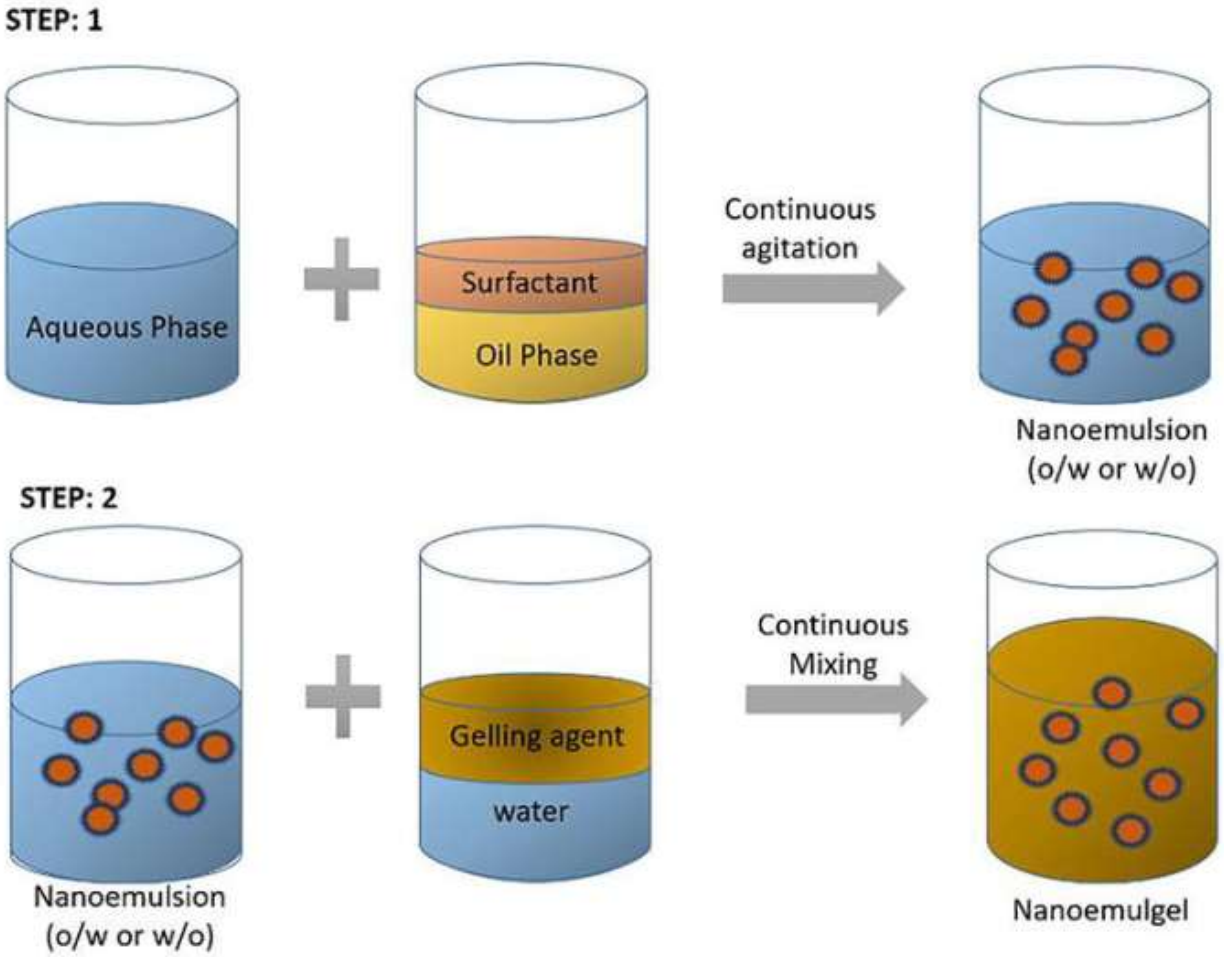

FIGURE NO. 5: FORMULATION PROCESS OF NANOEMULGEL

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