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A REVIEW ON NANOEMULSION BASED GEL

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ABSRACT
The advances in knowledge about production and stability of dispersed systems enable the development of differentiated vehicles such as nanoemulgel. Dermatological products applied to skin are diverse in formulation and range in consistency from liquids to powder but the most popular products are semisolid preparations. Topical gel are transparent or translucent semisolid formulation and used for the localized drug delivery anywhere in the body through rectal, vaginal, ophthalmic and skin as topical route. Gel formulation provides better application property and stability in comparision of cream and ointment. Nanoemulsion based gel is as one of the most interesting topical delivery system as it has dual release control system i.e. Hydrogel and nanoemulsion. Nanoemulgel having nanosize (10 -100µm) rapidly penetrates and deliver active substance deeper and quicker. The use of emulgels can be considered well in analgesics and antifungal drugs. In recent year there has been great interest in the use of novel polymer with complex function such as emulsifiers and thickeners. The gelling capacity of this compound allows the formulation of stable emulsion and creams by decreasing surface and interfacial tension at the same time increasing the viscosity of aqueous phase. In spite of many advantage of gels a major limitation is in the delivery of hydrophobic drug. So to overcome this limitation an emulsion based approach is being used to that even a hydrophobic moiety can enjoy the unique property of gel.

KEYWORDS: Nanoemulgel, Nanoemulsion, Hydrogel, Skin, Hydrophobic Drugs.

INTRODUCTION

The skin provides an effective barrier to protect the body from the penetration of molecules and micro-organisms in the external environment, and from excessive loss of water to maintain homeostasis. The main skin barrier resides in the stratum corneum due to its unique structure of layers off attened corneocytes surrounded by lipid bilayers composed primarily of ceramides. Penetration of most topically applied compounds follows the tortuous route of the stratum corneum lipid bilayers(intercellular), although the transcellular route through the corneocytes may contribute in some circumstances. Although hair follicles (and associated sebaceous glands) and sweat glands account for only about 0.1% of the total skin surface area, these appendages are potential routes of accessinto the skin, and may be important for nanosystems. Compounds that successfully diffuse across the stratum corneum are typically relatively small(up to about 500 Da), lipophilic (logP 1–3) and water soluble, thus excluding many potentially useful therapeutic compounds with properties that do not fit these criteria. A range of micro- and nanosystem shas been investigated as potential delivery vehicles that could enhance the skin penetration of both small and macromolecules that do not otherwise permeate the stratum corneum in sufficient quantities to provide a therapeutic outcome. Here, we review micro and nanosystems that have been applied to Pharmaceutics.[1,4]

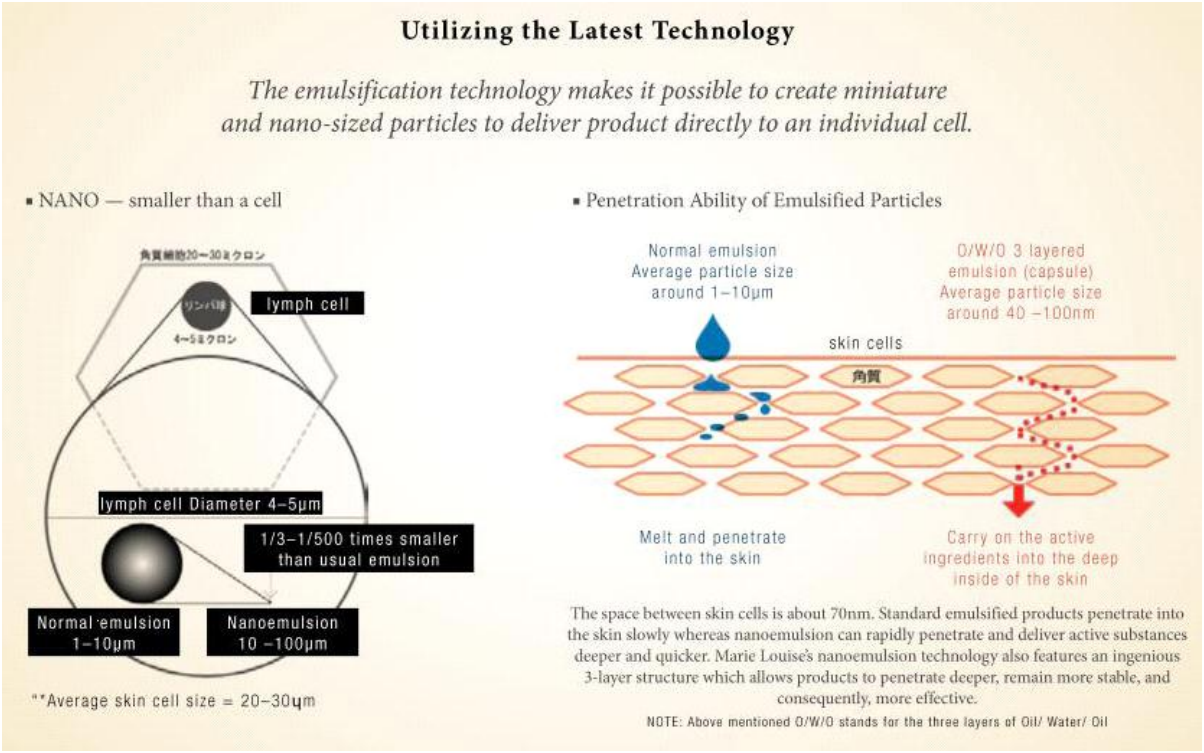

Fig 01: Nanoemulsion.

Advantages of Transdermal Preparations

Delivery of drugs through skin has certain merits and some of them are.

Convenient and pain free administration.

Avoid first pass hepatic effect.

Cost effective.

Drug can be delivered at predetermined controlled manner.

Potent drugs can be delivered through this route.

In case of emergency, patch can be removed easily.

Drugs with low therapeutic index can also be delivered through this route.

Disadvantages of Transdermal Preparations

Inspite of its potential to deliver the drugs through skin barrier, it has some inherited limitations and some of which are.

Drug loading is a limiting factor.

Not all the drugs can be delivered through this route.

Drugs which need high blood supply cannot be delivered through this route.

Due to the slow penetration, fast onset of action is not possible.

Special equipments and technology is required to manufacture TDDS.[5-7]

PROPERTIES OF IDEAL DRUG FOR TRANSDERMAL DELIVERY INCLUDE

· Molecular weight should be less than approximately 1000 Daltons.

· Affinity for both lipophilic and hydrophilic phases. Extreme partitioning characteristics not ideal.

· Low melting point.

· Should be potent, with short biological half- life and be non-irritating.

EMULSION

Emulsions are biphasic system in which one immiscible liquid is dispersed into other; due to this the system becomes unstable which is stabilized by emulsifying agents.

Emulsion can be either

- o/w
- w/o

GEL

The term "gel" represents a physical state with properties intermediate between those of solids and liquids. However, it is often wrongly used to describe any fluid system that exhibits some degree of rigidity. A gel consists of a polymer which swells in the presence of fluid and perhaps it within its structure. The rigidity of the gel is determined by the amount of fluid it entraps. These gels are wet and soft and look like a solid material. These are capable of undergoing large deformation in their physical state i.e. from solid to liquid.[8]

TYPES OF EMULGELS

Macroemulsions gel

These are most common type of emulgels where theparticle size of droplets of emulsion is more than 400nm. They are visually opaque but the individualdroplets can be easily observed under microscope. Macroemulsion are thermodynamically unstable, butcan be stabilized using surface active agents.

Nanoemulgel

When nanoemulsion is incorporated into gel it is called as nanoemulgel. Nanoemulsions are thermodynamically stable transparent (translucent)dispersions of oil and water stabilized by an interfacial film of surfactant and cosurfactant molecules having a droplet size of less than 100 nm. Nanoemulsion formulations possess improvedtransdermal anddermal delivery properties in vitro aswell as in vivo. Nanoemulsions have improved transdermal permeation of many drugs over the conventional topical formulations such as emulsionand gel

Microemulsion gel

Microemulsions are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they do not coalesce Microemulsions are composed of oil, surfactant, cosurfactant and water in specific proportions. The ingredients of microemulsion could facilitate the permeation rate of the drug by reducing the diffusion barrier of the stratum corneum.[9]

NANOEMULSIONS

Nanoemulsions are isotropic dispersed systems of two non-miscible liquids, normally consisting of an oily system dispersed in an aqueous system, or an aqueous system dispersed in an oily system but forming droplets or other oily phases of nanometric size. They are thermodynamically unstable systems, in contrast to microemulsions, because some nanoemulsions need high energy to produce them. They are susceptible to Oswald ripening and as a consequence susceptible to creaming, flocculation, and other physical instability problems associated with nanoemulsions. Despite this, they can be stable (metastable) for long periods due to their small size and the use of appropriate surfactants. Amphiphilic drugs can be formulated in nanoemulsions. They are nontoxic and nonirritant systems, and they can be used for skin or mucous membranes and parenteral and non-parenteral administration in general, and they have been utilized in the cosmetic field. These can be prepared by various methods which include three methods mainly: high-pressure homogenization, microfluidization, and phase-inversion temperature. Transdermal delivery using nanoemulsions has limitations due to the stability issues inherent to this dosage form. There are various commercial products available in the market some e.g. of drugs using nanoemulsions for transdermal drug delivery are gamma tocopherol, caffeine, plasmid DNA, aspirin, methyl salicylate, insulin and nimesulide. Presently, transdermal nanoemulsion formulations are not developed as much as nanoparticles or liposomes due to the inherited stability problems. The use of these nanocarriers to deliver analgesics, corticosteroids, anticancer agents, etc, is very important, as these drugs are able to act immediately because they do not need to cross extra barriers.[10]

FORMULATION OF NANOEMULSION

Nanoemulsion is prepared by using methods i.e. phase inversion technique and self emulsifying system. Formations of pre-nanoemulsion mixtures is neccesory before they could be self-emulsified in water under gentle, to produce nanoemulsion at room temperature.

A series of mixture of combination of oil phase, surfactant and co-surfactant are prepared to produce nano emulsion. A pseudoternary phase diagram is constructed based on the oil, surfactant and co-surfactant at a constant temperature to produce nanoemulsion. For each phase diagram, oil and specific Smix (surfactant and co surfactant) ratio were mixed thoroughly in different volume ratios in different glass vials. The Smix ratios are selected to reflect increasing concentrations of co surfactant with respect to surfactant for detailed study of the phase diagrams in the nanoemulsion formulation. Slow titration with the aqueous phase is performed for each combination of oil and Smix separately. For each Smix ratios, a separate phase diagram is constructed. Pseudoternary phase diagram with first axis representing the aqueous phase, second representing the oil phase and third representing a mixture of surfactant and co surfactant at a fixed volume ratio are constructed. Hence the various formulations of nanoemulsions are produced by pseudoternary phase diagram.[1]

METHOD

There are several steps involved in formulation of nanoemulgel first formulation of nanoemulsion. Second formulation of hydrogel using thickening agent, which increase the consistency of any dosage form. Finally nanoemulgel is prepared by the incorporation of nanoemulsion into hydrogel.

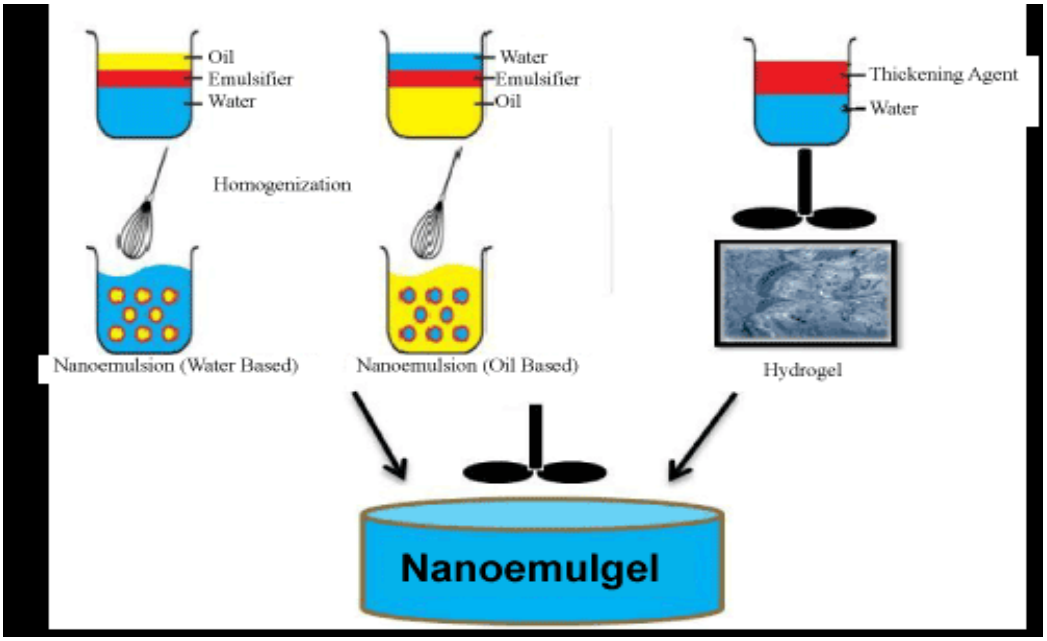

Fig 02:- Method of preaparation of Nanoemulsion.

COMPOSITION OF NANOEMULGEL

Oil
Surfactant/Cosurfactant
Aqueous phase
Gelling agent

Oil

Oils may be used to solubilize the lipophilic drugs and increasethe drugtransport through intestinal lymphatic system. Choice of oil component can modulate the topical drug delivery from O/W and W/O nanoemulsions.[21] Long and medium chain triglycerides oils with different degree of saturation have been used as oil phase, although the latter are preferred and are safe.

Surfactants (surface active agents)

Surfactant molecules consist of two parts, polar and nonpolar. They are classified according to the nature of polar group within the molcule into: anionic, cationic, non-ionic & zwitteri onic surfactants, Surfactants contribute Significantly in the formulation of nanoemulsions by lowering the interfacial tension between w/o immiscible liquids and make them miscible. They decrease the stress required to break the drop loweing the Laplace pressure. Further, they prevent to coalescence of newly formed drop. Hydrophile–lipophile balance (HLB) and critical packing parameter (CPP) must be taken into account or surfactant selection. Surfactants with low HLB (3–6) may be used to prepare w/o nanoemulsions whereas surfactants with high HLB (8–18) are used to.

Cosurfactants

A single chain surfactant alone may not be able to reduce the oil/water interfacial tension sufficiently for preparing nanoemulsions, hence arises the need of cosurfactants. These are ampiphilic in nature with a tendency to partition in large amounts at the surfactant interfacial monolayer. They reduce interfacial tension by increasing the fluidity of the interface and entropy of the system. HLB of the system can be modified by proper selection of surfactants and cosurfactants.

Additives: Additives are added to make the nanoemulsions last for longer periods.

Aqueous phase: The size of the droplets and stability of nanoemulsion may be affected by the nature of the aqeous phase. Careful consideration should be given to pH and presene of electrolytes in aqeous phase during nanoemulsion preparation.

Permeation enhancer: Permeation enhancers are partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. e.g. Oleic acid, lecithin, isopropyl myristate, urea, eucalyptus oil, chenopodium oil, pyrrolidone, laurocapran, dimethyl sulphoxide, linoelic acid, menthol.

PROPERTIES OF PENETRATION ENHANCER

They should be non-irritating, non-toxic and non allergenic.
They ideally work rapidly and the activity and duration of effect should be both predictable and reproducible.
They should have no pharmacological activity within the body i.e. should not bind to receptor sites.
They should work unidirectionally i.e. should allow therapeutic agents into the body whilst preventing the loss of endogenous material from the body.
Penetration enhancers should be correct for formulation into diverse topical preparations, so they should have compatibility with both excipients and drugs.
They must be cosmetically suitable with an appropriate skin 'feel'.[11]

METHODS OF NANOEMULGEL

High pressure homogenization
Microfluidization
Phase inversion method
Sedimentation

PHYSIOLOGY OF SKIN

There is most of the topical preparations are meant to be applied to the skin. So, there should be basic knowledge of the skin and its physiology function are very important for designing topical. Skin covers a surface area approximately $2m^2$ of an average of adult body and receives about one third of the blood circulating through the body. An average human skin surface is known to contain, the average 40-70 hair follicles and 200-300sweat ducts on every square centimetre of the skin. The pH of the skin varies from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of the skin surface. The skin can be considered to have four distinct layers of tissue as shown in figure.

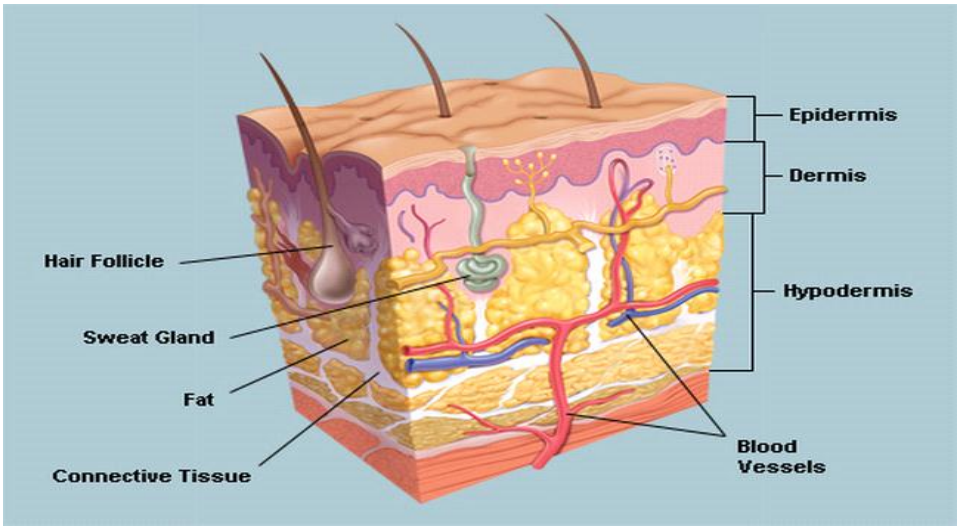

Fig no. 03: Physiology of skin.

The Epidermis

This is a stratified squamous epithelium layer i.e. composed primarily of two types of cells: keratimocytes and dendritic cells. Epidermis layer harbour a number of other cells such as melanocytes, Langerhans cells and Merkel cells. But the keratimocytes cells types comprises the majority of the cells by far.

Non-viable epidermis

stratum corneum is the outer most layer of skin, which is the actual physical barrier tomost substance that comes in contact with the skin. The stratumcorneum is 10 to 20 cell layer thick over most of the body.

Viable epidermis

This layer of the skin is in between the stratum corneum and the dermis and has a thickness of ranging from 50-100 µm. The structures of the cells in theviable epidermis are physiochemically similar to otherliving tissues. Cells are held together by to no fibrils. The density of this region is not much different thanwater. The water content is about 90%

Dermis

Just beneath the viable epidermis is the dermis. It is astructural fibrin and very few cells are like it can befound histological in normal tissue. Dermis thicknessranges from 2000 to 3000µm and consists of a matrixof loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance.

Subcutaneous connective tissue

The subcutaneous tissue or hypodermis is not actuallyconsidered a true part of the structured connectivetissue which is composed of loose textured, white, fibrous connective tissue containing blood and lymphvessels, secretary pores of the sweat gland and cutaneous nerves.[12, 13]

ROUTES OF DRUG PENETRATION THROUGH THE SKIN

There are basically three ways through the intact barrier may be identified i.e. the intercellular route, transcellular route and follicular penetration. The intercellular lipid route lies between the corneocytes, interlamellar regions in the stratum corneum, which has less ordered lipids and more flexible hydrophobic chains. Fluid lipids in skin barrier are important for transepidermal diffusion of the lipidic, hydrophilic and hydrophobic molecules migrating through intercellular lipid layers of such molecules. The transcellular route contemplates the crossing through the corneocytes and the intervening lipids. Intracellular macromolecular matrix in the stratum corneum does not contribute directly to the skin. diffusive barrier but supports in mechanical stability. Transcellular diffusion is as such not important for transdermal drug transport.

Recently, follicular penetration has become a major focus of interest due to the fact that drug targeting to the hair follicle is of great interest in the treatment of skin diseases. However, follicular orifices occupy only 0.1% of the total skin surface area. For this reason, it was assumed to be a non-important route for drug penetration. Such follicular pathways have also been proposed for topical administration of polystyrene nanoparticles.

FACTORS AFFECTING TRANSDERMAL PERMEABILITY

I. Physico-chemical properties of the penetrant molecules

1. **Partition coefficient:** Drugs having both lipid and water solubilities are favorably absorbed through skin. Transdermal permeability coefficient shows a linear dependency on partition coefficient. A lipid /water partition coefficient of one or greater is generally required.
2. **pH conditions*:*** The pH value of higher or very low can be destructive to the skin. With moderate pH values the flux of ionisable drugs can be affected by changes in pH that alter the ratio of charged and uncharged species and their transdermal permeability.
3. **Penetrant concentration*:*** Increasing concentration of dissolved drug causes a proportional increase in flux. At higher concentration, excess solid drug function as reservoir and help to maintain a constant drug concentration for a prolonged period of time.

II. Physico-chemical properties of drug delivery systems

1. Release characteristic*:* Solubility of the drug in the vehicle determines the release rate. The mechanism of drug release depend on the following factors.

a) Whether the drug molecules are dissolved or suspended in the delivery system,
b) The interfacial partition coefficient of the drug from the delivery system to skin,
c) pH of the vehicle,

2. Enhancement of transdermal permeation: Majority of drugs will not penetrate the skin at rates sufficiently high for therapeutic efficacy. The permeation can be improved by the addition of permeation enhancer into the system.

III. Physiological and pathological condition of skin.

1. Reservoir effect of horny layer*:* The horny layer especially is deeper layer, can sometimes act as a depot and modify the transdermal permeation of drugs. The reservoir effect is due to irreversible binding of a part of the applied drug with the skin.

2. Lipid film*:* The lipid film on the skin surface acts as a protective layer to prevent the removal of moisture from the skin and helps in maintaining the barrier function of stratum corneum.

3. Skin hydration*:* Hydration of stratum corneum can enhance permeability. Skin hydration can be achieved simply by covering or occluding the skin with plastic sheeting, leading to accumulation of sweet. Increased hydration appears to open up the dense, closely packed cells of the skin and increases its porosity.

4. Skin temperature: Raising the skin temperature results in an increase in the rate of skin permeation; this may be due to availability of thermal energy required for diffusivity.

5. Regional variation*:* Difference in nature and thickness of the barrier layer of skin causes variation in permeability

6. Pathological injuries to the skin*:* Injuries that disrupt the continuity of the stratum corneum, increases permeability due to increased vasodilation caused by removal of the barrier layer.

7. Cutaneous self metabolism*:* Catabolic enzymes present in the epidermis, may render the drug inactive by metabolism and the topical bioavailability of the drug.[14, 15]

CHARACTERIZATION OF NANOEMULGEL

Drug content determination

The amount of drug contained in the prepared nanoemulgel was determined by diluting required amount of prepared formulation using phosphate buffered saline (PBS) 7.4. This mixture was analyzed by UV spectrophotometer at 240 nm against PBS 7.4 as blank.

pH determination

Since the formulation was a topical formulation to be applied to the skin, therefore pH measurement was essential to ensure non irritating nature of the formulation. The pH of the formulation was determined at ambient temperature with digital pH meter (Rolex, India).

Spreadability

The Spreadability of prepared nanoemulgel was determined 48 h after preparation by measuring the spreading diameter of nanoemulgel between the two glass plates after 1 min. A weight of 350 mg of nanoemulgel was placed within a circle of diameter 1 cm pre-marked on the glass plate over which a second glass plate was placed. The increase in diameter as a consequence of weights added leading to spreading of gel was noted. The Spreadability can be calculated by using the formula,

Where, S = Spreadability, m = Weight placed on upper slide,

l = Length of upper slide and t = The time taken.

Droplet size, polydispersity and zeta potential of Nanoemulsions

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.

Viscosity measurements and rheological behavior

A Brookfield LVT DV-II Programmable Viscometer of Engineering Laboratories, Inc., (Middleboro, MA, USA) 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.

Ex vivo drug permeation studies

The ex vivo permeation studies were carried out using Franz diffusion cell, which is a reliable method for prediction of drug transport across the skin. These studies were conducted employing excised skin of Wistar rats. The hair on the dorsal side of the sacrificed animal was removed with a surgical blade no. 24 in the direction of tail to head. The shaven part of the animal skin was separated, excess fat and connective tissue were removed using scalpel. The excised skin was washed with normal saline, examined for integrity and subsequently used. The receptor compartment of the diffusion cell was filled with 20 mL phosphate buffer pH 7.4. Assembly was fixed on a magnetic stirrer and the solution in the receptor compartment was constantly and continuously stirred using magnetic beads at 100 rpm and the temperature was maintained at 37 ± 0.50°C throughout the experiments. The skin was mounted on diffusion cell assembly with an effective diffusion area (orifice area) of 4.91 cm2. The prepared formulation (1 g) was applied onto the membrane in donor compartment. An aliquot of 2 mL sample was withdrawn at a suitable time intervals and replaced immediately with an equal volume of fresh diffusion medium. Samples were analyzed spectrophotometrically. The drug permeated per cm2 of membrane was calculated and plotted against time and the flux was calculated as drug permeated per cm2/h.

Comparison of permeation studies of marketed

Formulation, optimized nanoemulgel, nanoemulsion, plain drug gel and drug solution. The ex vivo permeation study of 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 (Jss mg/cm/h) through skin was calculated from the slope of the linear portion of plotted curve. The lag time (Tlag) was determined by extrapolating the linear portion of the cumulative amount permeated versus time curve to the abscissa. Enhancement ratio (Epen) was calculated by dividing Jss of respective formulation with Jss of control formulation.

The amount of piroxicam retained in the skin was determined at the end of the experiment. Skin was removed where effective permeation of skin was cut, washed 3 times with saline solution and washed off. The sample of skin was homogenized in 1 mL methanol. Resulting solution was centrifuged at 3000 rpm for 10 min and analyzed for retention. Local accumulation efficiency (LAE) was obtained as the ratio of drug accumulated in the skin to that delivered through the skin.

Release kinetics

To study the release kinetics, data obtained from ex vivo permeation studies were fitted in various kinetic models: Zero order as cumulative percent of drug released versus time, first order as log cumulative percentage of drug remaining versus time and 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 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 slab matrix, if the exponent is 0.5, then diffusion mechanism is fickian; if $0.5 < n < 1.0$, mechanism is non-fickian.

Stability studies at different temperature conditions

Temperature stress studies were conducted by storing the formulation at different temperature conditions. Each formulation was stored in sealed glass containers in refrigerator (4°C), at ambient temperature (25°C) and at accelerated temperature (40°C) for 90 days. After 1, 7, 14, 21, 30, 45, 60 and 90 days, the formulations were evaluated for any physical change (such as clarity, phase separation, precipitation of drug, color change), drug content and pH.

Stability studies

All experimental measurements were performed in triplicates. Result values were expressed as the mean value ± standard deviation. Statistical analysis of difference in steady state flux and ex vivo permeation among predetermined intervals between formulations was performed by using unpaired t-test. The level of significance was taken at $P < 0.05$.[16-20]

MARKETED PREPARATION

DRUG	PRODUCT NAME	MANUFACTURER
Diclofenac diethyl amine	Voltaren emulgel	Novartis Pharma, India
Meloxicam	Meloxic emulgel	Provet

CONCLUSION

Nanotechnology based drug delivery systems are useful functional tools that had wide use in the pharmaceutics and therapeutics. The versatility and multi-functional characteristics of these nano systems makes them capable of alleviating the undesirable properties of drug molecules. As the most desirable attribute for a drug carrier is its ability to deliver drug to the targeted site, nanosystems are potent enough for the same. Thus, diverse nanosystems implied for transdermal delivery of drugs in view of approaches like nanoparticles, nanoemulsions, nano-implants, liposome, dendrimers and carbon nanotubes etc. would be a versatile means of constructing a new class of novel transdermal drug delivery systems.

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