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EFFECTIVENESS OF TOPICAL NANOEMULGEL IN PROMOTING WOUND HEALING

S. Venkateswara Rao[1*], G. Sandhya Vani[1], Ch. Kiranmai[1], K. Padmalatha[2]

[1*]Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh-521102, India. email- venkateshsadhu@gmail.com
[2]Department of Pharmacology, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh-521102, India.

***Corresponding Author:** Dr. Sadhu Venkateswara Rao
*Professor & HoD, Department of Pharmaceutics, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada, Andhra Pradesh, India.

Abstract
Wound healing is a complex and dynamic process involving various cellular and biochemical events. Over the years, researchers have explored innovative approaches to enhance wound healing and reduce the associated complications. One such promising advancement is the utilization of topical nanoemulgels, a combination of nanoemulsion and hydrogel, for promoting wound healing. This review systematically examines the various formulation components and techniques employed in the preparation of nanoemulgels, emphasizing their role in optimizing drug delivery to the wound site. Special emphasis is placed on the role of surfactants, co-surfactants, and polymers in optimizing the formulation to achieve enhanced stability, drug loading capacity, and sustained release profiles. Furthermore, the physicochemical attributes of nanoemulgels, such as particle size, viscosity, and rheological behavior, are dissected in detail. The impact of these properties on drug release kinetics and skin permeation is expounded. Moreover, this review critically assesses the future perspectives and applications of topical nanoemulgels for wound healing applications. In conclusion, this review provides a comprehensive overview of the formulation and evaluation of topical nanoemulgels for wound healing. The integration of nanotechnology with wound care holds promise for revolutionizing treatment strategies, offering faster healing, reduced scarring, and improved overall patient outcomes. Nanoemulgels provides sustain release activity and may be useful in solving the limitations of conventional drug delivery system. Patient compliance will be more because topical administration of these nanoemulgels is less greasy, transparent and comfortably applied on the skin.

Key Words: Wound healing, Nanotechnology, Hydrogel and Sustained Release.

INTRODUCTION

The restoration of normal function and structure following skin damage is facilitated by a dynamic and complicated biological process known as wound healing, which involves the coordinated activity of numerous cellular processes (Eming, S.A, *et al*., 2014). Multiple processes, such as hemostasis, inflammation, proliferation, revascularization, and remodeling, work together to close open wounds and restore normal function. (Landén, N.X, *et al*., 2016). In order for wounds to heal correctly, these stages must occur in concert and at just the right intensity. (Reinke, J, *et al*., 2012). Since there aren't

many effective medical treatments for wounds right now, research into novel methods of speeding up the healing process is urgently needed.

Anti-hyperlipidemic drugs called statins are commonly prescribed to patients for the prevention of cardiovascular problems. (Mooradian, A.D, *et al*., 2019). Recent studies have demonstrated that statins are effective in treating a wide range of dermatological conditions, from urticaria and psoriasis to acne. (El-Korashi, L, *et al*., 2018). It has been proposed that statins, due to their pleiotropic properties, can aid in wound healing by regulating cellular processes like inflammation, apoptosis, and proliferation. (Suzuki-Banhesse, V.F. *et al*., 2015) Also, they may have a role in facilitating and speeding up the healing process due to their ability to reduce oxidative stress and boost endothelial and microvascular functioning. (Choudhury, H, *et al*., 2017). Statins including simvastatin, atorvastatin (ATR), and pravastatin have been the subject of multiple research examining their effects on the healing of skin lesions. (Suzuki-Banhesse, V.F. *et al*., 2015). ATR, a second-generation synthetic statin, consistently showed the best outcomes in wound healing due to its combination of these desirable characteristics: prolonged protein binding affinity, lipophilicity, short half-life, and active metabolites. (Neuvonen, P.J, *et al*., 2006).

Oral statins cause myopathy and liver damage, among other negative consequences. When it comes to wound healing, a topical medication distribution method in the past proposed as a viable option choice other than oral statin because to its superior drug delivery, longer duration of action, and reduced side effects. (Farsaei, S, *et al*., 2012) Drugs can be applied directly to the skin using transdermal patches, gels, or emulgels. (Malvey, S *et al*., 2019). It has been revealed recently that nano emulgel, a unique approach for application of hydrophobic pharmaceuticals to the skin, offers various desirable advantages such heightened physical toughness, absence of toxicity, and absence of irritancy. (Choudhury, H, *et al*., 2017). It has a split release control mechanism consisting of a hydrogel and a nano emulsion, and it uses nano-sized particles to allow for rapid penetration and delivery of active medicinal components. The aforementioned properties of the nano emulgel allow for greater medication effectiveness in treating a variety of skin conditions and bacterial and fungal infections than is possible with more conventional formulations. (Mahtab, A, *et al*., 2016). In order to accomplish this, the current study set out to a variety of ATR topical formulations utilizing emulgel, and nano emulgel delivery systems.

Atorvastatin calcium is a widely prescribed drug belonging to the statin class, primarily used for the management of hypercholesterolemia and decreasing the risk of cardiovascular illness. Therapeutic benefit is achieved through inhibition of the enzyme HMG-CoA reductase. which is essential for the production of cholesterol. While the oral route is commonly employed for atorvastatin administration, topical formulations have gained focus because of the possibility of targeted medicine delivery, reduced systemic side effects, and improved patient compliance. Studies have suggested that atorvastatin can modulate various cellular processes involved in wound healing, such as inflammation, angiogenesis, and extracellular matrix remodeling (Bellosta, S, *et al*., 2018). However, its application to wounds is limited by factors such as poor aqueous solubility and limited bioavailability.

The development of a topical gel-based formulation loaded with atorvastatin calcium can offer several advantages. However, the challenges associated with its low aqueous solubility, poor skin penetration, and rapid metabolism necessitate the utilization of advanced drug delivery systems. Nanogels, also known as nanoparticulate hydrogels, have emerged as promising carriers due to their unique properties, including high drug loading capacity, tunable particle size, and sustained release profiles. Nanogels provide a controlled and sustained release of therapeutic agents. By encapsulating Atorvastatin calcium within a nanogel matrix, the release kinetics of the drug can be tailored, allowing for a prolonged and targeted delivery to the wound site. This controlled release profile ensures a consistent therapeutic concentration at the site of action, maximizing its effectiveness in promoting wound healing. Topical nanogels, offer convenience and improved patient compliance compared to systemic administration. By developing an Atorvastatin calcium nanogel for topical application, patients can easily apply the gel directly to the wound, leading to improved adherence to the treatment regimen and better wound healing outcomes.

TOPICAL DRUG ADMINISTRATION

Topical drug delivery is one of the widely researched topics as it offers non-invasive method of drug delivery, overcomes many disadvantages with other routes and offers many advantages like systemic route of drug delivery, overcomes enterohepatic circulation, etc. TDDS has become a choice of delivery system for many categories of drugs like insulin, hormones, pain killers etc. Other important advantage of TDDS includes long term delivery and controlled drug delivery. The major barrier in the delivery of drugs through transdermal route is the barrier effect of skin, small molecules with low molecular weight can easily diffused into the skin whereas the passage of large molecules is hindered by the skin. To overcome this effect many techniques and alterations are proposed some of them are as follows.

Active delivery

Active delivery indicates that energy in any either physical or chemical form is applied to enhance the transdermal delivery. Some of the most widely used techniques are

Iontophoresis

Iontophoresis involves the application of external stimuli in the form of electricity potential. As the potential gradient increased the penetration of the drugs was also shown to increase. The major advantage of this system includes that the dosage penetration can be dependent on the voltage applied which can be modified according to the patient needs. The disadvantage of the system is only ionic and non- ionic drugs can be made permeable.

Sonophoresis

Sonophoresis involves the application of sonication principle to enhance the permeation of the drugs. Generally low voltage sonication is applied as it creates a pocket which increases the diffusibility and intercellular spaces among the epidermal cells. Many drugs irrespective of the size and ionization constant can be permeated by using this technique. The major disadvantage in this is it causes slight burning of the skin.

Electroporation

Electroporation is a technique in which high voltage electricity is introduced a pulse on the skin which creates a pore through which the drugs irrespective of the molecular weight can be permeated. Major disadvantages include the permanent damage of the skin cells and denaturation of proteins.

Photomechanical waves

A laser of low power mechanical waves is put on the skin which leads to ablation which in turn increases the penetration of the drugs. Large molecular weight drugs like proteins can also be incorporated by using this route.

Microneedle

Microneedle approach indicates the administration of the drug directly into the epidermis with micro shaped needle. The microneedle approach is widely in use and research is going on regarding the structure and fabrication of the needle. Many approaches are in research in preparation of the microneedle like lazer metal cutting, 3D printing etc. The microneedles are also incorporated in various needs such as a simple delivery device, drug coated, dissolving microneedles etc.

Thermophoresis

Thermophoresis also called as thermal ablation process in which high temperatures are applied locally on the skin for a small time to disrupt the upper layers of keratin and care is to be taken not to disrupt the epidermis. This technique offers advantages of controlled delivery and improved patient compliance. The thermal ablation is caused by lasers of different radiofrequencies.

Liquid Jet

In liquid jet system high pressure jet is used to penetrate the drugs directly into the epidermis. The amount of drug entered into the body depends upon many physical factors like jet velocity, temperature, viscosity and pharmacological factors like thickness of the skin, age of the patient etc.

Passive delivery

Passive delivery indicates the usage of chemical substances that increases the solubility of the drug which in turn increases the permeability through skin. There are many chemical substances and drug delivery systems which are in current research and are showing promising results. Some of the inventions are

Vesicles

Vesicles are a type of colloidal particle that are characterized by the presence of ampiphilic compounds. These substances have the capability of increasing the solubility of the material. Vesicles offer many advantages like topical delivery, controlled drug release, systemic drug delivery and prolonged drug delivery for many days and weeks. Based on the structural composition the vesicles are categorised into various systems like liposomes etc. Liposomes are phospholipid bilayer molecules with either single layer or many layers; these are instantenously formed in an suitable environment. The liposomes offer many advantages like wide variety of solubility, usage in topical and systemic administration. Transferosomes are another modification of vesicles in which the single phospholipid layer is used and the major advantages include the flexibility of the phospholipid layer and many advancements are in progress in the design of the transferosomes. Next major type of vesicle is the ethosomes in which the water is an essential component of the vesicle as the lipid head is started with alcohol or water, the penetration capacity has been increased many times and the aqueous solubility of the drugs is increased.

Nano emulsion

Nano emulsion is an emulsion system stabilised by an interfacial membrane, comprises of oil phase in small globules. Nano emulsion offers many advantages over normal micro emulsions in increased thermal stability, and high permeability, overcome RES and wide variety of administration of drugs, phyto constituents etc. Nano emulsions can also include multiple emulsion systems which offer particular specifications which are in need for specific drugs.

Polymeric Nanoparticles

Nanoparticles are in usage in pharmaceutical science for various advantages like escape from RES and less dosage. The nanoparticles are used widely in targeted dosage forms. The nanoparticles are stabilised by using many natural polymers like polylactic acid, glycolic acid etc. The stabilized nanoparticles showed increased shelf life when compared to other dosage forms.

EMULGEL

Emulgels are a type of topical drug delivery vehicle that combine the benefits of gels with emulsions, with the emulsion utilized being either a type W/O or O/W. The inclusion of the water phase containing the gelling ingredient changes the emulsion into an emulgel.(Panwar, *et al.*, 2011). Emulgel's many benefits for dermatological use include its ease of application, lack of greasiness, thixotropy, water solubility, removal, shelf life, lack of discoloration, and biocompatibility.

NANOEMULGEL

Nanoemulgels, which are gels that include nanoemulsions, are created when the Nanoemulsion system is intergraded into the gel matrix to improve skin permeability. (R Sigh, 2014). This nanomulgel slurry can be thought of as a reservoir for the drug, regulating its distribution from the inner to the outside layer. When applied to healthy skin, a nanoemulgel breaks down into oil droplets that can then penetrate the skin's superficial layers (SC) and deliver the medicine where it's needed. Nanoemulsion-gels are particularly effective in penetrating the skin because of their high solubilizing

of the medication within the oil state, which creates a bigger a change in the concentration in the direction of the skin. Additionally, patient compliance is enhanced as a result of the reduced stickiness and increased spared ability in comparison to creams and ointments.

Nanoemulgel's Advantages:

1. The dispersion of oil droplets in a Gel foundation increases the stability of nanoemulsions; in this case, the drug's affinity for the oil is what determines the nanoemulsion's stability. (Joshi Baibhav, *et al*., 2011).
2. As the medication goes downward along the concentration gradient created by its strong adhesion and solubilizing capability, it becomes more effective at penetrating the skin.
3. Furthermore, these formulations improve patient adherence and facilitate the transfer of lipophilic and poorly water-soluble medications.
4. Drugs with a shorter half-life can also benefit from the regulated release provided by nanoemulgel.
5. The formulation should be more easily spreadable than creams.
6. Nanoemulgels are completely safe and non-irritating.
7. When compared to other formulations, this one has a higher drug loading.
8. Improve medication absorption and skin penetration.

Rational

The use of topical dosage forms, such as creams, lotions, and ointments, might have serious implications. There are a number of drawbacks, including the fact that it is sticky, difficult for patients to use, has poor spreading capabilities, and necessitates excessive rubbing to be effective. Likewise, there were red flags raised regarding the stability of the formulation for hydrophilic drugs. These problems are shared by the majority of semisolid preparations, which is why gelled formulation has become increasingly popular in both medicinal and aesthetic applications. Surface tension holds liquids in place inside a macromolecular network of fibers formed from a gelling substance. Hydrophobic distribution of medications, while helpful, presents a substantial obstacle. To get around this issue, an emulsion-based technique can be employed to introduce the lipophilic medicinal moiety into the gel-based system. (S Pant, *et al*., 2015).

METHODS OF FORMULATION

Nanoemulsion-gel formulations typically consist of the following substances:

a. Component testing
b. Nanoemulsion Manufacture
c. Nanoemulgel production.

a. Component testing:

Solubility of drugs was tested by adding excessive amounts adding different oils and then agitating them for three days to achieve equilibrium. The soluble was calculated using the centrifuged supernatant from the samples. Then, the most drug-soluble excipients from each class are chosen for additional testing. (R Shankar, *et al*., 2015).

i. Diagram of a psedoternary phase: Different ratios of surfactant to cosurfactant (N mix) were used (2:1, 3:1, and 5:1). For the purpose of examining phase diagrams, various ratios of surfactant to co-surfactant were selected, increasing in surfactant concentration. Here, distilled water is used as the diluting medium within the aqueous phase. Different mixes were prepared by mixing oil and mix in varying proportions, from 9:1 to 1:9. The diagrams that emerge from this study will be used primarily for identifying phase boundaries. It was created using the titration method, utilizing water as the aqueous medium. Nanoemulsion transparency is determined by slow titration of oil and mix and ocular inspections. The three phases of a nanoemulsion are the aqueous phase, the oil phase, and the N mix (surfactant and co-surfactant). (J Modi, *et al*., 2011).

b. Formulation of Nanoemulsion: In order to create a Nanoemulsion of a specific drug, first the medicine is dissolved in oil; then, the oil is combined with the Nmix. and last the combination is diluted with water.

c. Formulation of Nanoemulgel: A gel basis can be made by dissolving 1 g of Carbopol in the amount of water. The generated Nanoemulsion is added gradually after the Carbopol solution has been stirred for 24 hours and has fully swelled and dispersed. When Triethanolamine is added to a gel, the gel is distributed evenly throughout. Distilled water is used to fine-tune the final amount. Figure1.

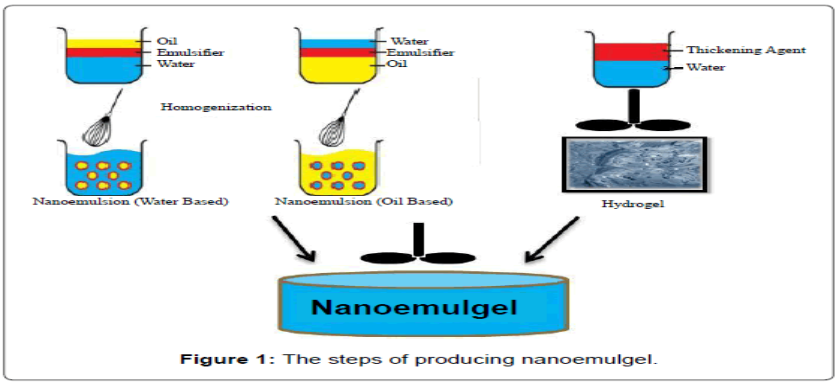

Figure 1: The steps of producing nanoemulgel.

COMPONENTS OF NANOEMULSION

Nanoemulsion is made up of these primary elements:

Oil: To obtain a stable nanoemulsion in which the highest amount of medicine might solubilize, oil phase selection is the most crucial characteristic. (Mangale MR, *et al*., 2008). When creating nanoemulsions, Since oils are excellent solvents, they are frequently used when selecting a medication candidate. This allows for a higher concentration of drugs within the nanoemulsions. (Debnath S, *et al*., 2011). To maximize drug solubility, a combination of oils can be employed. Nanoemulsion oils are a blend of several oils. list in Table 1 below

Table - 1: List of oils used in nanoemulsion

Oils	Botanical Names
Peanut oil, or Arachis oil.	Arachis hypogaea
Brahmi oil	Bacopa monnieri
Clove oil	Syzygiumaromaticum
Linseed oil (Flax seed oil)	Linumusitatissimum
Oil of eucalyptus	Eucalyptus globules
Jojoba oil	Buxus chinensis
Peppermint oil	Mentha piperita
Neem oil	Azadirachta oil
Tea tree oil	Melaleuca alternifolia

Table - 2: List of surfactants used in nanoemulsion

Surfactants	Chemical Names
RH 40 Kolliphor	hydroxyl group of macrogolglycerol
Acid ursolic	Ursenic acid, 3-hydroxy-12-, 28-dihydro,
Labrafil M 1944 CS	Polyoxyl-32 oleoylglycerides
Lauroglycol FCC	Monolauric acid propionate
PEG MW>4000	Polyglycerol, carbowax
PlurolOleique CC 497	Poly(3-oleoyl)glyceryl dioleate
Poloxamer 188	A polymer made up of blocks of poly(ethylene glycol), poly(propylene glycol), and poly(ethylene glycol).

Surfactant: The stability of the nanoemulsion system relies heavily on surfactants. There are three types of surfactants used here; anionic, cationic, and nonionic. Due to their dissimilar chemical natures, surfactants (Table 2) must be carefully chosen if a stable delivery system is to be achieved. Surfactants with the right HLB value are needed to create a stable nanoemulsion. (Mangale MR, *et al*., 2008).

Cosurfactant: The polarity of the surfactant must be lowered by the addition of cosurfactant in order to create a stable nanoemulsion. Cosurfactants (Table 3) act on the surfactants' interface and include alcohols with chain lengths ranging from C3 to C8. In order to achieve a stable formulation, these aid in boosting oil penetrability. (Debnath S, *et al*., 2011).

Aqueous phase: The stability of a nanoemulsion and the size of its droplets were most affected by the composition of the aqueous phase. Physiological environments span a wide pH spectrum, from 1.2 (stomach) to 7.4 (blood) and beyond. The characteristics of nanoemulsions can also be significantly altered by the presence of different ions in the physiological environment. (Debnath S, *et al*., 2011).

EVALUATION OF NANOEMULGEL

Methods that are used to define nanoemulgel formulations

Physical and chemical constants:

A visual examination is performed on colors, consistency, phase separation, and the like in the generated nanoemulgel compositions. (Dev A, *et al*., 2015).

Estimating PH:

It is possible to measure the final formulations' pH levels. Here, a 250-ml beaker is used to hold the formulations while the pH meter is submerged in the solution. Three times through the procedure, the exact same formulation is used. (Lakshmana PS, *et al*., 2017).

Research on Rheology:

Cone and plate viscometers or Brookfield viscometers fitted with the proper spindle are used to measure the viscosity of various nanoemulgel compositions in a thermostatically-regulated 25°C water bath with aeration. (Debnath S, *et al*., 2011).

Distribution of nanoemulgel globule sizes:

Malvern zetasizer is used to analyze the size and dispersion of globules. A 1g sample is mixed with sterile water until it is evenly dispersed. By injecting a sample into the photocell of a zetasizer, one can learn about the typical globule size and distribution. (Soujanya C, *et al*., 2014).

Coefficient of dispersion:

The device for measuring spreadability comprises of a pulley and a wooden block. Nanoemulgels' spreadability is evaluated using their 'Slip' and 'Drag' properties. On this square, you'll find a ground glass slide. This ground slide has a lot of the nanoemulgel (2 grams or so) that is being studied on it. Once the nanoemulgel has been prepared, it will be placed between two glass slides. For 5 minutes, we press the slides together with a 1 kg weight to remove air and spread the nanoemulgel into a homogenous layer between the glass. The amount of time it takes for the top slide to move 7.5 cm when 80 g is supplied to the system is recorded in seconds. (Lakshmana PS, *et al*., 2017).
The formulas determine that a lower interval is a better indicator of spreadability:
$S=M.L/T$
Where, S=Spreadability,
M=Mass of the Top Slide, and
L= Length of slide, respectively.

T = amount of time needed to completely untangle the slides.

Tests for extrudability in tubes:
This test measures the force required to extract the substance from the tube. Extrudable nanoemulgel yield from a collapsible metal tube with a lacquer finish is measured in grams, and the time it takes to extrude a ribbon of nanoemulgel measuring at least 0.5 centimeters in width is recorded. Extrudability improves with increased output [25]. Following this, the extrudability can be determined with the use of the following formula.
Extrudability = Extruded nanoemulgel weight (in g)/Extruded nanoemulgel area (in cm2).

Drug content determination:
An adequate combination of a nanoemulgel formulation with an appropriate solvent to yield the desired drug content. Drug concentration is then estimated by uv spectrophotometry using the same standard plot by entering the absorbance value as provided by More et al. after the solution has been filtered via whatman filter paper. (Lakshmana PS, *et al*., 2017).

Patch test for skin irritants:
After applying the solution to the rat's freshly shaved skin, look for any untoward changes in color or texture in the next 24 hours. The test is successful if no irritation develops. (Bhagat KA, *et al*., 2015).

***In vitro* release study**
Franz diffusion cells (effective diffusion area: 3.14 cm2, cell volume: 15.5 ml) are used in studies of drug release. After clamping the diffusion cell shut between the donor and the receptor chambers, the nanoemulgel is evenly distributed throughout the dialysis membrane. The drug is dissolved in phosphate buffer saline (pH 5.5) solutions and then administered into the receptor chamber. The receptor chamber's contents are stirred with a magnetic stirrer. To ensure accuracy, 1.0 ml aliquots are taken at regular intervals. Samples are diluted appropriately, and their drug concentration is checked using UV visible light. Clearance of drugs over the dialysis membrane can be determined. (Bhagat KA, *et al*., 2015).

Kinetics of Drug Release:
Topical information release data on nanoemulgel will be used to investigate the drug-delivery mechanism. (Srivastava M, *et al*., 2014). using the following set of equations:
Zero-order equation:

$$Q=K0t$$

Where Q is the amount of drug released at time t, and K0is the zero-order release rate.
First-order equation:

$$\text{In } (100\text{-}Q)=\text{In } 100 - K1t$$

Where Q is the percentage of drug release at time t, and K1 is the first-order release rate constant.
Higuchi's equation:

$$Q=K2\sqrt{t}$$

Where Q is the percentage of drug release at time t, and K2 is the diffusion rate constant

Stability studies
After generation, the nanoemulgels are stored in 5 g aluminum collapsible tubes and evaluated for stability at 5 °C, 25 °C, 60% RH, 30% RH, and 40% RH for a period of three months. The appearance, pH, rheological features, drug content, and drug release profile of samples are evaluated every 15 days. Studies of the stability of gel-filled nano emulsions at high speed Studies of stability are conducted in accordance with ICH recommendations. For three months, we keep the concoctions in a temperatures of 37°C, 45°C, and 60°C in a hot air oven. Every two weeks, samples are examined using a UV-Visible spectrophotometer to determine the medication content. The pH of a formulation is monitored throughout time to determine its stability. (Sharma BR, *et al*., 2016).

CONCLUSION

In conclusion, this review provides a comprehensive overview on topical nanoemulgels for wound healing. The integration of nanotechnology with wound care holds promise for revolutionizing treatment strategies, offering faster healing, reduced scarring, and improved overall patient outcomes. Nanoemulgels provides sustain release activity and may be useful in solving the limitations of conventional drug delivery system. Patient compliance will be more because topical administration of these nanoemulgels is less greasy, transparent and comfortably applied on the skin.

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