Recent Analysis on new Nanoemulgel Transdermal Drug Delivery System use for Skin Disease Treatment

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Article History:
Received on: 09 Nov 2020
Revised on: 14 Dec 2020
Accepted on: 20 Dec 2020

Keywords:
Nanoemulsion, emulgel, Nanoemulgel, drug delivery framework

ABSTRACT
Nanoemulsions have the potential in medical industries due to transparency at high droplet volume division, higher bio availability rate and expanded shelf life of drugs. The “Nano emulsion-based gel” is a very interesting transdermal delivery framework as it has double delivery control framework, i.e., nano emulsion & hydrogel. The Nano emulgel having nanosized emulsion goes from 10-100 μm may quickly enter and convey dynamic substance more profound and faster. The gelling limit of this compound permits the definition of stable emulsion and creams by diminishing surface and interfacial pressure simultaneously expanding the consistency of watery stage. Regardless of the many preferred position of gels, a significant restriction is in delivery of hydrophobic medication. So to defeat this constraint, an emulsion-based methodology is being utilized to that even a hydrophobic moiety might appreciate exceptional property of gel. They have clingy causing distress, less spreading coefficient, scouring is a requirement for application to the skin, and they show the issue of solidness for detailing. Due to all these disadvantages, gels are selected for both cosmetic as well as a pharmaceutical formulation. Despite several benefits of gels, the main drawback is with the delivery of hydrophobic therapeutic moiety. So, emulgel based approach is used to overcome this drawback; by this, even a hydrophobic drug might be included and delivered successfully. When emulsions and gels are mixed than that dosage form is mentioned as emulgel. In fact, the existence of a gelling agent changes conventional emulsion into an emulgel in the water phase.

INTRODUCTION
Nanoemulsions are the novel medication delivery framework that permits continued or controlled release of medication such as genetic materials & biological active ingredient and so on. The Nanoemulsion contains oil, surfactant and a fluid stage, and they are isotropically clear and thermoprogressively stable fluid arrangement, ordinarily with bead width in the scopes of 10 – 500nm (Suyal et al., 2018). Numerous skin specialists, like moisturizer, salve, cream are generally utilized have dif-
ferent hindrances. These emulgel have various benefits over novel drug delivery systems as well as on conventional drug delivery systems in numerous aspects. One of the promising ways for drug organization is skin due to accessibility of huge surface region (Patel et al., 2014; Venkataharsha et al., 2015; Allen and Ansel, 2013). Medication conveyance through the skin to the foundational dissemination is advantageous for various clinical conditions because of which there has been an impressive enthusiasm for this zone. It offers the benefit of consistent state-controlled medication conveyance over a broadened timeframe, with self-organization additionally being conceivable, which may not be the situation with a parenteral course (Verma et al., 2018).

**Nanoemulsion and Nanoemulgel**

Nanoemulsions are isotropic scattered frameworks of two non-miscible fluids, ordinarily comprises of a slick framework scattered in a watery framework, or a watery framework scattered in a sleek framework however shaping beads or other slick periods of nanometric size. Nanoemulsion-gel has a decent bond and high solubilising property, the medication in the oil stage prompts bigger fixation inclination towards the skin that further increment skin entrance of medication. Likewise, understanding consistency is improved because of expanded spared ability, diminished tenacity contrast with creams and balms (Pattanayek and Puranik, 2018).

**Types of Nanoemulsion**

Depending on composition

1. **O/W Nanoemulsions**: oil droplets are dispersed in a continuous water phase.
2. **W/O Nanoemulsions**: water droplets are dispersed in the continuous oil phase.
3. **Bi-continuous Nanoemulsions**: water and oil are dispersed with each other (Choudhary and Fátima, 2017)

**Components of Nanoemulgel**

**Oils**

Oils utilized in Nanoemulsion are commonly mineral oils utilized as the vehicle for drugs, e.g. Castor oils and different fixed oils (maize oils, cottonseed oil, Arachis oil) Olive Oil, eucalyptus oil, Coconut Oil, rose oil, clove oil and so on.

**Aqueous Phase**

For the organization of hydrogel & nanoemulsion, refined water is utilized as an aqueous stage.

**Surfactant and Co-Surfactant**

Surfactants are utilized both to give emulsification at the hour of definition and control everyday dependability during the time frame of realistic usability of arranged nanoemulsion. E.g. Range 80 (Sorbitanmonoooleate), Polyethylene-glycol-40-stearate, Labrasol, Stearic corrosive, PlurolOleique, Tween 80 (Polyoxyethylene-sorbitan-monooleate), Labrafil, Sodium stearate, Where specialists like Transcutol, Captex, Cammul, Miglyol, and so on can be used as co-surfactant or co-solvents.

**Gelling Agent**

Polymers are basic to give the basic organization for the planning of gels are known as gelling specialists, e.g. Common - Agar, Tragacanth, Guar gum, Xanthan Gum, Semi-engineered and Synthetic Carbapol, Poloxamer, HPMC (cellulose subsidiaries).

**Permeation Enhancers**

They communicate with various skin constituents to deliver a reversible temporarily increment in penetrability (Pattanayek and Puranik, 2018).

**Advantages of Nanoemulsion**

1. Increases bio availability.
2. Enhances the absorption rate.
3. Gives aqueous dosage form for water-insoluble drugs.
4. Eliminates variability in absorption.
5. Quick and effective penetration of drug moiety.
6. Nanoemulsion formulation required less amount of surfactant compare
7. Nanoemulsions are the thermodynamically stable framework, and stability
8. Nanoemulsion is not exposed to attack by air & water.
9. Less amount of energy requirement (Bhatt et al., 2013)

**Disadvantages of Nanoemulsion**

1. Nanoemulsion is having the inadequate solubilizing capability for high melting substances.
2. The high concentration of co-surfactant & surfactant and essential for solubilizing the nanodroplets.
3. Nanoemulsion stability is affected by environmental factor like Ph & temperature.
4. The surfactant should be nontoxic for utilizing pharmaceutical application (Mahajan and Savale, 2016)

Application
Topical Delivery
Topical organization of medications might have benefits over diverse techniques for some reasons; it will evade the hepatic first-pass metabolism of medication and related toxicity impacts. They directly target & delivery medication to the influenced area of eyes or skin.

The nanoemulsion might accomplish an elevated level of effective antimicrobial action is recently proficient by fundamental anti-toxins. The nanoemulsion has extensive range movement against microscopical organisms (like S. aureus, E.coli,) growths (like Dermatophytes, Candida) (Gadkari et al., 2018; Choudhary and Fátima, 2017).

Antimicrobial activity
Essential oil like Thymus daenensis produces nanoemulsion which is generally used as antibacterial and also increase the ability nanoemulsion of Thymus daenensis essential oil created by high-intensity ultrasound method signifies bigger antibacterial activity with enhanced capability to disrupt cell membrane integrity of E.coli, a food-borne pathogen.

In Cosmetic
Nanoemulsions are used for lipophilic drug transport and it also helps the skin penetration of active ingredients & hence enhances their concentration in the skin (Jivani et al., 2018). Recently significance of nanoemulsions has become enhancing as best vehicles for cosmetics controlled delivery and for optimized dispersion of active ingredients in specific skin layers.

In nanoemulsion there is no sedimentation, inherent creaming, flocculation is noticed with macro emulsion, so nanoemulsion is acceptable in cosmetics.

Nanoemulsion to improve skin penetration
The organic solvents have been utilized to upgrade the skin infiltration of poor efficacious medications. Yet, these solvents actuate some antagonistic impacts on the skin, for example, skin disturbance, poisonousness and refinement. To evade these unfriendly impacts, the drug is captured in the o/w nanoemulsion without utilizing skin natural solvents. Furthermore, o/w nanoemulsion permits high solvent limit with regards to water-insoluble topically dynamic medicaments and furthermore helps in conveying water; a magnificent conditioner, to the skin, e.g. Diazepam, NSAIDs, α-tocopherol, antifungal medications ( econazole or miconazole nitrate).

Transdermal Drug Delivery (TDD) System
The TDD might be described as the application of a medication to skin for local or systemic action (Barakat et al., 2011). They are recognized to remove oral gastrointestinal (GI) adverse effects and handle the level of plasma drug for a longer time and appropriate for chronic disease’s long treatment of (Rehman and Zulfakar, 2014).

The TDD frameworks are a stable source of interest due to the advantages they afford in overcoming numerous disadvantages connected with other drug delivery modes (i.e., intravenous, oral). Due to skin impermeable nature, designing a proper drug delivery vehicle”, which penetrates the skin barrier is challenging (Shankar et al., 2015).

REVIEW OF LITERATURE
Drais et al, investigated Piroxicamnanoemulsion gel of as topical dosage form to enhance the solubility of Piroxicam & diminish gastrointestinal side effect, which intend to increase therapeutic activity & Piroxicam bioavailability in Table 1. They resulted in pseudo- ternary phase plot that has a big area of nanoemulsion is surfactant mixture ratio (3:1) and used for nanoemulsion formulas further to formulate nanoemulsion gel. They finished that nanoemulsion gel is an effective alternative for Piroxicamtropical delivery (Karthikeyan et al., 2012).

Karthikeyan et al, developed nanoemulsion coating by using Azadirachta Indica (neem oil) as substitution of organic solvent, utilizing neem oil & tween 20 as an emulsifier. They reported mean droplet size ranging from 31.03 - 251.43nm.

Then the prepared stable emulsion loaded for coating on steel surface by using method electrophoretic deposition method, the atomic force microscopy images the formulation confirmed the nano emulsified coated on steel (Khullar et al., 2012).

Khullar et al, developed emulgel by using Mefenamic acid as a model drug. They used Carbopol 940 as mentha oil, gelling agent and clove oil as penetration enhancers.

The formulations are assessed for rheological surveys, bio adhesion strength, spreading coefficient surveys, in-Vitro release, skin irritation studies, and reported that Mefenamic acid topical emulgel possess an effective analgesic activity & anti-inflammatory (Gupta et al., 2015).
| Sl. No. | Drug     | Oil             | Surfactant      | Co-surfactant | Method              | Report                                                                 |
|--------|----------|-----------------|-----------------|---------------|---------------------|------------------------------------------------------------------------|
| 1.     | Ketaconazole | Myritol 18      | Kolliphor HS 15 | PEG 200       | Aqueous titration method | Nanoemulsion of Ketacanazole can be used for topical application for fungal diseases. ([Aggarwal et al., 2014](#)) |
| 2.     | Piroxicam | Oleic acid      | Tween -80       | Ethanol       | Aqueous titration    | The new piroxicam nanoemulsion gel with appropriate viscosity and utilized for transdermal application ([Pratap et al., 2012](#)). |
| 3.     | Carvedilol | Oleic acid, IPM | Tween 20        | Carbitol      | Spontaneous emulsification | Nanoemulsion have enhanced bioavailability for transdermal and eliminate first-pass effect ([Shafaat et al., 2013](#)). |
| 4.     | Clozapine | Oleic acid      | Tween 20        | Transcutolp   | Spontaneous emulsification | Nanoemulsion have significantly enhanced bioavailability for transdermal and eliminated first-pass metabolism ([Chaudhri et al., 2015](#)). |
| 5.     | Amisulpride | Oleic acid, IPM | Labrasol, Tween-20 | PEG-400     | Ultrasonic method    | Nanoemulsion showed significant increases invivo bioavailability ([Vijaya et al., 2015](#)). |

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Table 1 continued

| 6.     | Micanazole nitrate | Clove oil | Tween 20 | Ethanol | Spontaneous emulsification | Nanoemulsion was stable at room temperature and effectively delivered micanazole transdermally compared with marketed gel (Perane et al., 2018). |
|--------|--------------------|-----------|----------|---------|----------------------------|--------------------------------------------------------------------------------------------------|
| 7.     | Etoricoxib, Methyl salicylate | Oleic acid | Tween 80 | Propylene glycol | Low energy method | Nanoemulgel is efficient, secure, & promising for inflammatory conditions treatment (Kaur, 2019). |
| 8.     | Mefanamic Acid | Capryol 90 | Tween 60 | Transcutolp | Aqueous titration method | Topical nanoemulgel of mefanamic acid be a promising choice over conventional topical formulation (Arora et al., 2014) |
| 9.     | Ketoprofen | Oleic acid | Tween 80 | Transcutolp | Titration method | New ketoprofen nanoemulgel with proper viscosity is effectively formulated for transdermal application (Nurdianti et al., 2018). |
| 10.    | Astaxanthin | Sunflower oil | Kolliphor RH40 | PEG 400 | Self-nano emulsifying (SNE) method | Nanoemulsion can serve as a potential vehicle for improved transdermal delivery of astaxanthin. (Drais, 2016) |
Brajesh et al., Developed nanoemulsion gel containing carvedilol for transdermal drug delivery system they used spontaneous emulsification method, after constructing a spontaneous ternary phase diagram. They have used oil, surfactant, co-surfactant and reported oleic acid act as a powerful enhancer of the transdermal drug delivery system. Further in their study, they have reported a mean droplet size of 71.8nm and then nanoemulsion formulation shows the highest flux at 24hrs. Finally, they have concluded that nanoemulsion gel formulation has a greater potential to improve the bioavailability of carvedilol by transdermal drug delivery framework (Thakkar et al., 2015).

Gupta et al., developed a nanoemulsion based transdermal patches of Diclofenac Diethylamine, by using solvent evaporation technique. Nanoemulsion was categorized for diverse physicochemical factors. They concluded that nanoemulsion comprising transdermal patches might be a promising device for improving Diclofenac Diethylamine percutaneous delivery.

Arora et al., developed nanoemulgel as a transdermal delivery framework for poorly water-soluble drug, Ketoprofen, to overcome problems related to its oral delivery. They constructed Pseudo-ternary phase diagrams utilizing titration technique to figure out the components concentration range. Their results revealed that nanoemulsion signified best physical stability during storage at room temperature with better antibacterial activity.

Thakkar et al., studied Itraconazolnanoemulsion by the method of speed stirring method, by using capmul mono-diglyceride of medium-chain fatty acid (MCM) C8 as oil, pluronic F68 as co-surfactant and cremophore EL as a surfactant, and then followed by sonication.

Sharma et al. developed nanoemulsion gel of Tenoxicam and reported the particle size with nano range. They used the emulsification method using ethyl oleate, tween- 80 and propylene glycol, surfactants and co-surfactants. They concluded that Tenoxicam has better efficacy and transdermal application.

Majeed et al., developed Eugenol loaded nanoemulsions, emulsified with changed starch by high-pressure homogenizer at 150Mpa pressure, 5processing cycles and study their apoptotic potential against liver and colon cancer cells and were surveyed in comparison with bulk eugenol. In this study, they concluded that reactive oxygen species perform the main role in apoptosis in HTB37&HB8065 cells.

Vatsraj et al., developed a new “oil-in-water (O/W) nanoemulsion” framework having the capability to function as a carrier for poorly soluble drugs with Clarithromycin as model antibiotic. They utilized “3-level 3-factorial central composite investigational design” to conduct investigates. They investigated selected variables effects, polysorbate 80, olive oil content & polyvinyl alcohol concentration. Their results revealed that nanoemulsion revealed best physical stability through storage at room temperature with better antibacterial activity.

CONCLUSION

The topical Nanoemulgels have demonstrated a better choice for compelling and helpful medication delivery framework—Nanoemulgel where medication is joined into oil period of Nanoemulsion and afterwards converged with a gel base. Nanoemulsion stacked gel gives higher viability in some effective issues. The eventual fate of Nanoemulsion-Gel based definitions may give a superior and dependable answer for the conveyance of hydrophobic medications. An extensive parcel of drugs used as a piece of the treatment of skin disease.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

Funding Support

The authors declare that they have no funding support for this study.

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