Original Article

An Update On Recent Advances In Nanoemulsion Based Hydrogels: Anoemulgels

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Abstract

The newly developed lipophilic drug molecules encounter problems like availability of less amount of drug at the site of action, unpredictable absorption, etc. To overcome these disadvantages, enhancement of solubility and development of novel formulation is a continuous process. Recent advances in technology had helped in developing novel nanoparticulate topical delivery systems. Their characteristic properties such as nano droplet size i.e. 20-200nm, high interfacial area, transparent, translucent appearance, capability to freely solublise in water, high kinetic stability, sedimentation, flocculation and coalescence created a new era in the development nanoparticulate topical drug delivery systems with increased applications. The most advantageous thing about topical nanoemulsion is that it can penetrate and permeate the skin membrane without incorporation of a permeation enhancer. Various studies revealed that the activity of anti inflammatory and anti fungal drugs have been increased as topical nano preparations i.e. nanoemulsions and nanoemulgels with compared to conventional emulsions and emulgels. Nanoemulgels are nanoemulsion based hydrogels prepared by adding nanoemulsion to the hydrogel matrix. The inability of hydrogels led to the development of nanoemugels which solublises the lipophilic drug in the oily phase of the emulsion followed by the addition of this mixture into a gel base.

Keywords: Nanoemulgels; Nanoemulsion; Lipophilic drug; Solubilty; Topical drug delivery systems; Phase diagram.

1. INTRODUCTION

Over the years oral administration has been preferred because of its properties such as patience compliance. Its limitations such as hepatic first pass metabolism results in intake of excessive drug dose, irritation of gastric region due to the existence of surfactants in oil base formulations, and the spread of drug in systemic circulation results in unavoidable after effects[1]. Therefore to avoid such undesirable side effects a non invasive, painless, non-irritating drug delivery system is developed i.e. topical drug delivery[2]. Topical delivery of drug helps to deliver drug to a specific site, reduces systemic toxicity, overcome presystemic metabolism and decrease in irritation of gastric mucosa [3].

The newly developed lipophilic drug molecules encounter problems such as availability of less amount of drug at the site of action, unpredictable absorption, variations between two subjects or within the same subject[4]. To overcome these disadvantages enhancement of solubility and development of a novel formulation is a continuous process. The solubility of a lipophilic drug can be enhanced by physical modification, chemical modification or development of a new formulation[5].

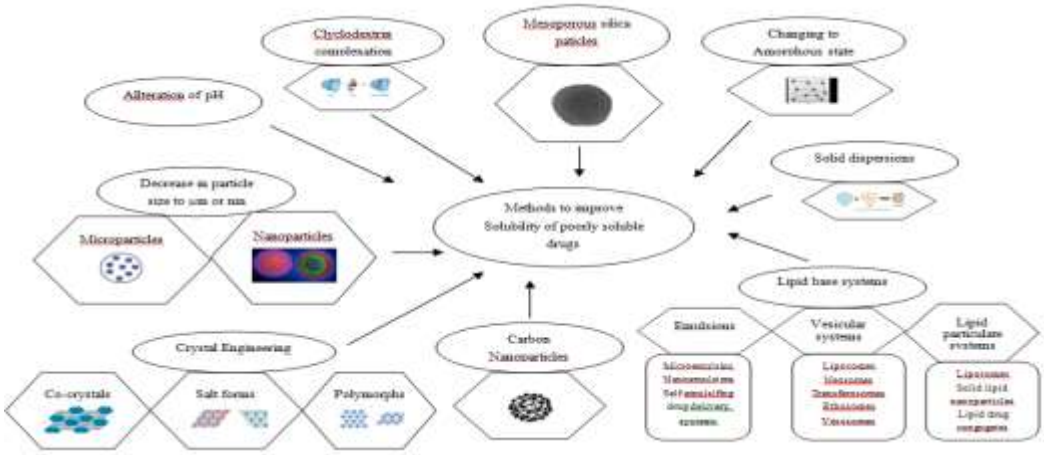


Fig 1: Methods to improve solubility and bioavailability of lipid soluble drugs.[7,39]

Recent advances in technology helped in developing novel nanoparticulate topical delivery systems. Their characteristic properties such as nano droplet size i.e. 20 to 200 nm, high interfacial area, transparent and translucent appearance, capability to freely solublise in water, high kinetic stability, sedimentation, flocculation and sometimes coalescence created a new era in the development nanoparticulate topical drug delivery systems with increased applications[6].

Besides these thixotropy, non-greasy, easy to spread and remove, external smoothening property, does not stain and non sticking, longer shelf life and biologically compatible are other improved characteristics of the novel nano particulate drug delivery systems[7].

Pharmaceutical nanoemulsions can be used to deliver drugs both orally and topically. They can also deliver parenteral nutrition. The most advantageous thing about topical nanoemulsion is that it can penetrate and permeate the skin membrane without incorporation of a permeation enhancer in its formula [8]. Various studies revealed that the activity of anti inflammatory and anti fungal drugs have been increased when they are given as topical nano preparations i.e. nanoemulsions and nanoemulgels when compared to conventional emulsions and emulgels[9].

Table 1: Differences between Microemulsion and Nanoemulsion

PARAMETERS	MICROEMULSION	NANOEMULSION
Size	200-1000 nm	20-200 nm
Shape	Spherical, lamellar	Spherical
Stability	Thermodynamically stable	Thermodynamically unstable but kinetically stable
Method of Preparation	Low energy Method	High and low energy methods
Polydispersity	Typically low (<10%)	Typically low (<10-20%)
Components	Oil, water, surfactant and possibly a co-surfactant	Same components of microemulsion, protiens and polysaccharides used as surface active agents
Surfactant/Oil Ratio	Large surfactant/oil ratio	Low surfactant/oil ratio
Optical Properties	Transparent	Transparent to opaque

Nanoemulgels are nanoemulsion based hydrogels prepared by adding nanoemulsion to the hydrogel matrix. The inability of hydrogels to transport lipophilic drugs led to the development of nanoemugels which solublises the lipophilic drug in the oily phase of the emulsion followed by the addition of this mixture into a gel base[10]. As a result, nanoemulgels can also be developed to improve the limitations of hydrogels, such as stability and delivery of lipophilic drugs topically [11]. The attention of many young researchers was drawn towards the development of numerous drugs into mixture of emulsion and gel delivery system used to treat various skin disorders. The addition of gelling agent to a nanoemulsion reduces the interfacial surface tension, enhances viscosity of the aquatic phase and therefore can be easily administered through topical route[12].

2. IMPORTANT CHARACTERISTICS OF NANOEMULGEL:

- **Stability:** The distribution of oil droplets into a gel base increases the stability of a nanoemulsion because of the enhanced affinity of drug towards oil.

- **Adhesion:** The adhesive property of the nanoemulgel and increased solubility results in high concentration gradient and enhances the penetration of drug into the deeper layers of the skin[13].

- **Controlled release:** Drugs with shorter half life can be formulated as controlled release nanoemulgels.

- **Non toxic and non irritant:** Nanoemulgels are less toxic and do not cause any irritation.

- **Permeability and Drug desorption:** The formulation of a drug as a nanoemulgel enhances permeability through skin and drug desorption[14].

3. FORMULATION OF A NANOEMULGEL:

A nanoemulsion weather w/o or o/w consists two main phases-oil and water. The phase that is present in less quantity is the dispersed phase and that is available in large quantity is continuous phase. The minute droplets of the dispersed phase are adjoined by a surface active agent whose activity is intensified by the incorporation of co-surfactant.

A study on the optimization of oil, utilizes certain innate characteristics of the selected oil which have been reported in the text below[15].

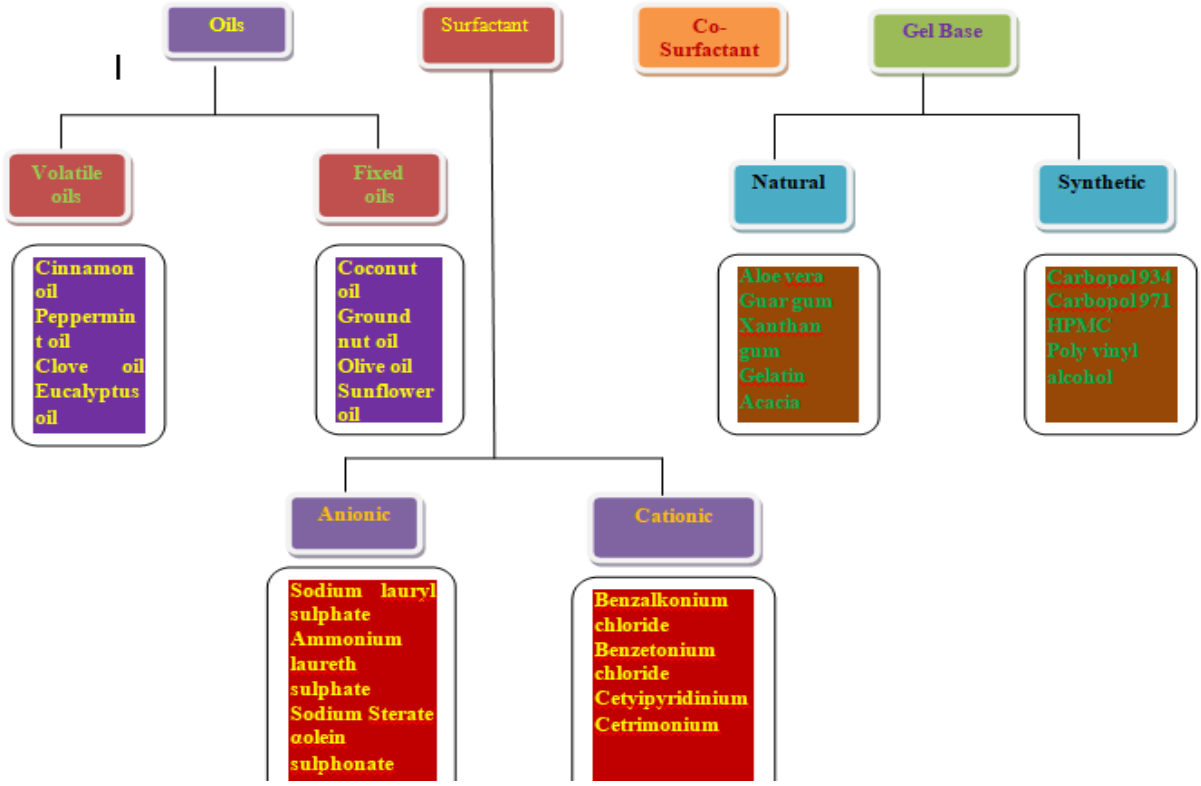


Fig 2: Important constituents of Nanoemulgel

3.1 Selection of Oil.

The most essential component of a nanoemugel is the lipid component, i.e. oil. Various studies reveal that the selection of oil phase to formulate a nanoemulsion is influenced by certain properties such as viscosity, permeability and stability. In case of natural oils the selection of oil is also influenced by their therapeutic property[16]. Vegetable oils such as soya bean oil, corn oil etc., containing long chain fatty acids results in an unstable emulsion because of poor emulsification properties[17]. Alternatively, oils with decreased hydrophobic property have better emulsification property and the ability to solubilise lipophilic active ingredient in oil is influenced by the increase in hydrophobicity of the oil. Therefore, the selection of lipid phase is a critical step in the preparation of nanoemulgel[18].

Table 2: Essential part, Biological source, important chemical constituents and medicinal uses of oils used in the preparation of Nanoemulgel

Volatile/Fixed oil	Essential part	Biological Source	Important Chemical Constituents	Medicinal use
Anise oil	Seeds	Pimpinella anisum	Anethole γ-himachalene	Diuretic Appetite stimulant Antifungal and anti bacterial.
Black seed oil	Seeds	Nigella sativa	Linoleic acid Oleic acid Margaric acid	● Anti asthmatic. ● Reduce cholesterol and high blood pressure. ● Anti diabetic.
Castor oil	Seeds	Ricinus communis	Ricinoleic acid Oleic acid Linoleic acid	Laxative Anti inflammatory Reduce Acne
Cinnamon oil	Dried inner bark and shoots of coppiced trees	Cinnamomum zeylanicum	Cinnamaldehyde Eugenol	● Has the ability to reduce cholesterol levels and Oxidative Stress. ● Reduces the Risk of Cancer.
Clove oil	Dried flower buds	Eugenia caryophyllus	Eugenol, β caryophyllene	Antimicrobial, NSAID for tooth ache and muscle pain. Relieve respiratory disorders
Olive oil	Ripe fruit	Olea europoea	Oleic acid Linoleic acid Palmitic acid	Anti inflammatory, In treatment against heart diseases and Alzheimer's disease
Peanut/arachis oil	Seed kernels	Arachis hypogaea	Oleic acid Linoleic acid Palmitic acid	Controls diabetes and lowers cholestrol
Palm oil	Fruits	Elaeis guineesis	Tocotrienol Palmitic acid Oleic acid	Preventing Vitamin A deficiency, Anti malarial Increases metabolism

Peppermint oil	Fresh flowering tops	Mentha piperita	Menthol Menthone	Relieves itching on topical application. Treatment of bowel syndrome and muscle pain.
Sunflower oil	Seeds	Helianthus annus	Linoleic acid Oleic acid	Emollient, Relieve constipation and decrease bad LDL.
Sesame oil	Seeds	Sesamum indicum	Linoleic acid Oleic acid Palmitic acid Stearic acid	Antioxidant Anti microbial Anti inflammatory
Soybean oil	Mature seeds	Glycine soja	Palmitic acid, Stearic acid, Arachidic acid,	Reduce cholesterol levels. Prevent bone loss.
Safflower oil	Ripe and dry seeds	Carthamus tinctorius	Tocopherol Linoleic acid	Improves blood sugar levels. · Lowers cholesterol.

3.1.1. Oleic acid.

Oleic acid is a monosaturated, omega-9 fatty acid which is occurring naturally. This is an odorless, colorless, biodegradeable and biocompatible oil originating from vegetable and animal products. The characteristics of oleic acid such as greater solubility, enhancement of percutaneous absorption, make it a suitable as oil phase in nanoemugels[19]. It posses antioxidant property that strengthens the integrity of the cell membrane by replacing the damaged cells and tissues. Therefore, because of these advantages oleic acid has been selected as the oil phase for preparing nanoemulgels to magnify the permeation of drugs via the skin[20].

3.1.2. Eugenol.

Eugenol is an essential oil extracted by distillation from Syzygium Aromaticum having antimicrobial, anti fungal, anti-inflammation activity. [21,22,23,24].

3.1.3 Tea Tree oil.

Tea tree oil is an essential oil obtained from Melaleuca alternifolia is a popular broad spectrum anti-microbial agent. Moreover it is used as an ingredient in the topical formulations to treat bacterial and fungal infections. [25,26].

3.1.3. Almond oil.

Tolnaftate controlled release nanoemugel prepared using oil extracted from Prunus amygdalus as lipid phase is given percutaneously for effective and prolonged treatment of fungal infection. The use of almond oil is also helpful in increasing the stability of the preparation [27].

3.1.4. Castor oil.

Castor oil obtained from Ricinus communis was preferred because of its Anti inflammatory and Anti fungal effect. Such therapeutic activities of castor oil were used by various researchers in formulation of nanoemugels of Oxiconazole and Epirnomectin[28,29].

3.2. Use of oil as active ingredient.

In some cases the oil itself is used as active ingredient or target compound for formulation of nanoemugel. One such example is Swietenia macrophylla oil nanoemugel shows higher anti-inflammatory effect than parent form[30].

3.2.1. Virgin coconut oil

Virgin coconut oil obtained from Cocos nucifera is used in as an active ingredient in the formulation of a nanoemulgel with increased bioavailability and improved the stability [31].

Table 3: Research work done using different oils and their Inferences

Author	Oil	Drug	Inference	References
Abdesh et al	Oleic acid	Aceclofenac	Enhanced permeation at low concentrations.	19
Bhavna, et al		Piroxicam	Permeation of drug into the lipid bilayers of the skin and enhances the drug's thermal behaviour in the skin.	21
M.Srivatsava, et al	Eugenol	Ketoprofen	Exhibits additive anti bacterial effect against E.Coli and S.Aureus	23
Shadab Md		Diclofenac Sodium	Increased permeation and showed anti inflammatory effect as well.	24
Ahmed et al		Thymol	Improving the topical efficacy of therapeutics by enhancing the percutaneous drug permeation to its higher concentration gradient.	25
M.A.Mirza	Tea tree oil	Itraconazole	Additive effect against Vaginal Candidiasis	26
P.N.Gadkari et al	Almond oil	Tolnaftate	Effective and prolonged treatment of fungal infection. Also helpful in increasing the stability of the preparation.	28
Ashwini V.K.et al	Castor oil	Oxiconazole	Anti –inflammatory and Anti fungal effect.	29

3.2.2. Edible oil or Vegetable oil.

Edible oil or Vegetable oil may not be the first line of choice in all cases due to its limitation such as low emulsification and inability to dissolve greater quantity of lipid soluble drugs. So, in order to overcome the draw backs of edible/vegetable drugs medium chain, mono, di or triglycerides are utilized as oil phase in the evolution of a formulation to transport class II drugs[32].

Medium chain triglycerides can encapsulate drugs having log P value in between 2 and 4. The best example for such oil is Labrafac which is used as oil phase in nanoemulsion preparation. Though different varieties of Labrafac are available, LipophilieWL1349, were used in the preparation of Ketoprofen nanoemulgel for transannular delivery [33].

Table 4: Chemical Constituents HLB value Applications of Edible or Vegetable oils used in Nanoemulgels

Lipid excipient	Chemical Constituents	HLB /SAP value	Applications
Labrafac™ lipophile WL 1349	Propylene glycol esters of caprylic (C_8) and capric (C_{10}) acids	1-2	Oil phase for topical formulations. Oily vehicle and solubilizer for solutions (parenteral, auricular)
Maisine	Mono, di and triglycerides of mainly linoleic($C_{18:2}$) and oleic ($C_{18:1}$) acids	1-2	Solubilizer for poorly soluble lipophilic API
Compritol®888ATO	Mono, di and triesters of behenic acid	2-3	Lipid carrier for preparation of nanoparticles
Capmul MCM	Glyceryl caprylate	3-4	Assists in the development of a emulsion, microemulsion or nanoemulsion to facilitate absorption
Peceol	Mono-, di- and triglycerides of oleic ($C_{18:1}$) acid	3-4	Solubilizer
Geleol™	Mono-, di- and triesters of palmitic (C_{16}) and stearic (C_{18}) acids	3-4	Lipidic vehicle and modified release agent
Captex 200	Propylene glycol dicaprylate	315-335 (SAP value)	Used to produce stable emulsions and to modify viscosity
Caproyl 90	Propylene glycol monocaprylate	5-6	Solubilizer in topical dosage forms.
Miglyol 812	Mixture of decanoyl- and octanoyl glycerides	325-345 (SAP value)	Excellent spreadability.
Lauroglycol™ FCC	Mono-, di- and triesters of palmitic (C_{16}) and stearic (C_{18}) acids	5-6	Solublizer and co-surfactant in topical dosage forms.

Another medium chain triglyceride that is commonly used for pharmaceutical purpose is Capmul MCM, having HLB value 5-6 and is readily soluble in water. It is non irritating and can be used as fat phase for occular nanoemulgel preparation [34]. Miglyol 812 can also be an oil of choice for occular nanoemulgel as it can be tolerated by human eye, and is non-irritant. But its use is restricted due to decreased Nanoemulsion region in pseudo ternary diagram.

This may be because of small alkyl chain and high molecular volume [35]. Maisine,a long chain triglyceride was used in the preparation of Carbamazepine loaded mucoadhesive o/w nanoemulgel for intra nasal delivery because of its advantages such as purity, stability and lymphatic absorption[36]. Captex 200 is a medium chain triglyceride used for preparation of Miconazole nanoemulsion by Shinde P.B because less quantity is sufficient for solublisation of drug, emulsification can be achieved with minimum amount of surfactant and no toxicity at higher concentration[37]. Caproyl 90 has been used as an oil phase for developing nanoemulsion for various lipid soluble drugs to improve their pharmacokinetic and pharmacodynamic properties. It has HLB value of 5 and due its lipophilicity, it can easily solublise the drug with less polar area[38]. Maha E. Elmataeeshy et.al. prepared Terbinafine nanoemulgel with enhanced transdermal permeability using Peceol as oil phase [39,40].

3.3 Selection of Surfactant.

Surfactants are the compounds that lower the surface or interfacial tension between two liquids or a liquid and a gas. It is the integral component of a nanoemulgel system used to stabilize the thermodynamically unstable mixture of two immiscible liquids by lowering the surface tension and changing the dispersion entropy[41].

3.3.1 Characteristics to be considered during Selection of a Surfactant.

- Safety and stability.
- Capacity to load the drug is high and good emulsifying property.
- Selected surfactant is to be absorbed at once onto the interface of the two phases that are immiscible dramatically preventing the coalescence of nano droplet [42].

3.3.2 Classification of Surfactants.

Surface active agents are classified based on their ionic nature as:

Anionic
They contain an anionic functional group i.e. negatively charged ions such as sulfate, sulfonate, phosphate etc on their hydrophilic head. E.g.:- Sodium laurly sulfate, Sodium Stearate[43,44].

Cationic
They contain a cationic functional group i.e. positively charged ions such as quaternary ammonium compounds on their head. Eg:- Benzalkonium chloride, Benzethonium chloride etc[45,46].

Non ionic
They have covalently bonded oxygen containing hydrophilic group bounded to hydrophobic parent structures. The capability of non ionic surface active agents to form a hydrogen bond decreases with enhancing the temperature and aqueous solubility. Eg:- Polaxomers, Glyceryl monosterate, Tweens.[47,48]

Table 5: Synonyms,Applications,HLB value and Manufacturers of Emulsifying agents

Type of Emulsifying agent	Surfactant	Synonyms	Application	HLB value	Manufacturers
O/W Emulsifying agent	Polysorbate 20	Tween 20 Alkest TW 20 Montanox 20	To stabilise suspensions and emulsions.	16.7	Dev International · Akhil Healthcare Private Limited Triveni Chemicals · Green Leaf Industries
	Polysorbate 60	Tween 60	Emulsification of cosmetics.	14.9	Sigma –Aldrich Sisco Research laboratories Pvt.Ltd
	Polysorbate 80	Montanox 80 Alkest TW 80 Tween 80	Emulsifier in oral and parenteral dosage forms	15	Akhil Healthcare Private Limited Ozar Care Exim Private Limited Dev International · Globedeck Overseas · Maya Chemtech India Private Limited.
	Labrasol	-	O/W surfactant for topical gels, nanoemulsions, microemulsion.	12	Gattefosse
	Kolliphor EL	Cremophor EL Macrogolglycerol ricinoleate, Macrogolglyceroli ricinoleas	Enhancement of solubility and emulsification.	12-14	Unichem Laboratories Limited BASF Corp
	Kolliphor HS 15	Solutol HS 15 Macrogol 15 Hydroxystearate	Potent emulsifier for parenteral, ophthalmic and topical preparations	16	BASF Pharma
	Koliphor RH 40	Macrogolglycerol Hydroxystearate	Emulsifier and primary surfactant used in parenteral and oral formulations.	14-16	BASF Pharma
	Gelucire 44/14	Lauroyl Macrogol-32 glycerides	Emulsifies in aqueous fluid into microemulsion or nanoemulsions	14	Gattefosse
W/O Emulsifying agents	Span 60	Sorbitan monosterate	Emulsifier for water-in-oil creams and lotions	4.7	Sigma –Aldrich Sisco Research laboratories Pvt.Ltd
	Span80	Sorbitan Monooleate	Emulsifier that promotes uniform distribution of excipients and prevent separation. Stabilize aqueous preparations for parenteral use	4.3	Sigma –Aldrich Sisco Research laboratories Pvt.Ltd

3.3.3. Mechanism
The repulsive forces between nano droplet and ionic charge present on the head of the surface active agent molecule and at the interface of the two immiscible phases prevent aggregation of droplets forming a nanoemulsion that is stable thermodynamically [49].

3.3.4. Selection of Surfactant.
Point to be remembered which selecting a surfactant.

Toxicity.
Usually irritation to the skin may be caused due to incorporation of large amount of surfactant topically and in the GI tract when taken in the mouth. So, a minimum quantity of surfactant has to be added into the dosage form[50,51].

HLB value.

Based on HLB value surfactants are classified into:

✓ W/O emulsifying agents: They have HLB value of 3-8. So surfactants having HLB value less than 8 are preferred.

✓ O/W emulsifying agents:- They have a HLB value of 8-16. Hence to develop a stable o/w nanoemulsion surfactants having HLB value greater than 10 are selected. Eg:-Tween& Spans with HLB>8[53,54].

In addition, a combination of these two contributed to greater stability of nanoemulsion when compared to pure Tween or Span because of minimum size of dispersed droplet[55].

Secondly, by mixing surfactants of high and low HLB values a nanoemulsion which is stable can be prepared. Ex:- Noor E L Din et al prepared a nanoemulsion of water in diesel by approximate mixing of low and high HLB surfactants Tween 80 having HLB 15, and Span 80 of HLB 4.3. These systems contains lipophilic and hydrophilic emulsifiers aligned along besides each other transmitting enhanced rigidity and strength to the film of emulsifier due to hydrogen bonding resulting in more stable nanoemulsion. They improve the stability by reducing the energy required to develop nanoemulsion.[56]

Table 6: Studies and observations on nanopreparations developed using different Surfactants

Author	Surfactant	Drug	Observation	References
Noor E L Din et al	Tween 80 and Span 80	Water in diesel	Transmitting enhanced rigidity and strength to the film of emulsifier due to hydrogen bonding resulting in more stable nanoemulsion. They improve the stability by reducing the energy required to develop nanoemulsion.	50
Asiya Mahtab	Tween 80	Ketoconazole	Invitro release and ex vivo permeation study of the optimized nanoemulgel showed better efficacies, and enhanced in vitro fungal activity when compared to drug suspension.	31
S Pund et al.	Cremophor EL	Leflunomide	Solubility of surfactant in lipid ingredient is in line with solubility of therapeutic agent	52
Bhavna et al.	Tween 80	Piroxicam	Showed higher cumulative amount of drug permeated and flux and significantly less drug retained along with less lag time than marketed formulation.	21
Paliwal et al.	Span 20	Terbinafine	Clear nanoemulsion was formed due to orientation of surfactant at the interface	54
Sanjeev R et al.	Solutol HS 15	Tenofovir	Physiologically compatible and decreased globule size.	55
Symala	Cremophre RH40	Butenafine	Prolonged skin permeation	56
Aparna et al.	Acrysol	Telmisartan	Enhanced skin permeation compared to other topical dosage forms	57

The nature of a surfactant is an important criterion to be considered while selecting a surfactant. Mostly non-ionic surface active agents are selected as they are biocompatible, harmless, and are not affected by changes in pH and ionic strength. The major drawback with ionic surfactant is toxicity [57]. In addition, the miscibility of oil with surfactant is to be considered for surfactant selection, i.e., researchers selected surfactant Cremophor EL because of its solubility in lipid ingredient in line with solubility of therapeutic agent such as Leflunomide[52]. Similarly,

Surface active agents that occur naturally are generally obtained from animals, bacteria, few yeast and fungi. The use of these surfactants is gaining more importance these days as they are less toxic, biocompatible and biodegradable. They are amphiphilic in nature and also help in reducing interfacial tension [58].

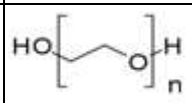
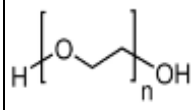
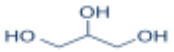
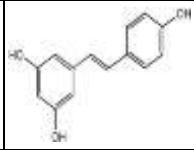
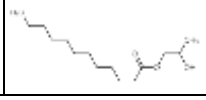
Bio-surfactants contain a head that is polar in nature and tail which is short and contains a fatty acid. It has affinity to both lyophobic and lipophilic drugs. Bai and Mc Clements utilized rhamnolipids as biosurfactant for development of nanoemulsion and observed that rhamnolipids to be superior natural surfactants which can be used in place of synthetic surfactants commercially [59]. Rosa et al prepared o/w emulsion using oil rich in d-tocotrienol and a extract of Brazilian ginseng root abundant in saponin as biosurfactant [60].

3.4 Co-Surfactant

Co- surfactant is a chemical substance used in conjunction with the surface active agent in the nanoemulsion to emulsify oil in water. Nanoemulsions are composed of a surfactant and a co-surfactant that helps the active ingredient to penetrate into deeper layers of skin, by disrupting the film at interface and imparting required fluidity. They also reduce the tension at interface by promoting emulsification [61]. They promote solublisation of oil by modifying the angle at oil-water interface. The lipophilic drug's release in both water and oil is affected by its partitioning, and selection of right co-surfactant is imperative. [62].

The concentration of co-surfactant affects the activity of the surface active agent during emulsification. The proportion of surfactant and co-surfactant to form a nanoemulsion depends on the dimensions of nanoemulsion area in the pseudo ternary phase diagram. The nanoemulsion area can be enhanced by increasing the length of carbon chain [63]. Bhavna along with her team studied that when only surfactant was used, a narrow nanoemulsion region was obtained which might be because of aggregation of surfactant. They further studied that addition of a co-surfactant in same concentration showed significant oil in water nanoemulsion area and on further increasing co-surfactant concentration to 1:2 ratio showed a much larger area for O/W nanoemulsion. This is due to enhanced penetration of the oily phase into the lipophilic part of the surface active agent by reducing the globule size of oil phase due to the use of co-surfactant. The increase in nanoemulsion area is a result of increase in entropy [21].

Table 7: Structure, solubility and HLB value of Co-Surfactants.

Co-Surfactant	Structure	Physical state and solubility	HLB value	Manufactures
PEG 400		Liquid, Very freely soluble in water and many organic solvents	11-12	Akzo Nobel BASF Pharma SABIC Shell Industries
PEG 200		Liquid, Very freely soluble in water and many organic solvents	6-8	Akzo Nobel BASF Pharma SABIC Shell Industries
Glycerol		Liquid, Freely soluble in water	3-4	Pure Chemicals Co Mohan Organics Pvt Ltd.
Stearic acid		Solid pellets	15-16	Ennore India chemicals Chirag Orgo Chem
Transcutol HP		Liquid, Soluble in common organic solvents and water.	-	Gattefosse
Lauroglycol		Liquid, Water insoluble	3-4	Gattefosse

Similarly, Bali et al prepared two formulations using Caproyl 90 as the lipid phase and different combinations of surfactant and co-surfactant like Labrasol and Transcutol P having low HLB and Tween 20 and PEG 400 with greater HLB value. They studied a considerable nanoemulsion area was observed when Tween 80, a surfactant with high HLB value is incorporated, but a reduction in nanoemulsion region was observed when co-surfactant of same quantity (1:1) was added. In the second preparation sufactant and co-surfactant of low HLB values were incorporated. In this preparation less quantity of oil was emulsified with high concentration of S_{mix} in equal ratio and noted a drastic increase in nanoemulsion area [64].

Shinde studied that formation of nanoemulsion is a result of concentration of components of the system. He observed nanoemulsion region in 1:1 proportion of S_{mix} due to decreased tension and increased fluidity at the interface. This ratio requires 30%W/W of S_{mix} for solublising 20% W/W of oil. When the concentration of surfactant is doubled a broader nanoemulsion region was obtained and a maximum of 28%W/W of S_{mix} was sufficient to solublise 20% W/W of oil. On further increase of surfactant: co-surfactant ratio to 3:1 a narrow nanoemulsion region was depicted. Therefore, it was studied that addition of double the amount of surfactant there was an increase in nanoemulsion area and on further increase of surfactant could not increase nanoemulsion area. After the screening of all the components, various ratios of S_{mix} were prepared. S_{mix} is prepared by enhancing the proportion of surfactant with respect to co-surfactant and vice versa. Then this S_{mix} was added to the selected oil in the ratio 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, and 1:9. The blend of oil and S_{mix} formed is assayed against water and the volume of titrant was noted. Finally, a ternary phase diagram was attained by taking oil, S_{mix}, and water on three axis to study the nanoemulsion region. [37].

Pseudo Ternary phase Diagram:

Phase diagram: Phase diagram is a diagrammatic representation of stability limits of various phases in a chemical system at equilibrium with respect to variables such as composition and temperature.

Pseudo ternary phase diagram: Pseudo ternary phase diagram is a tool to optimize the concentration range of the three components of a typical emulsion, i.e. oil, water and S_{mix} to obtain, a stable emulsion.

A pseudo ternary phase diagram is constructed using CHEMIX 10 software by taking oil, water and S_{mix} on the three axis to obtain the nanoemulsion area. The diagram of S_{mix} depicting greater nanoemulsion area helps to get the formula to prepare nanoemulsion.

4. PREPARATION OF NANOEMULGEL

The preparation of nanoemulsion is usually done in 2 steps:

4.1. Development of Nanoemulsion:

Drug is mixed in oil and then the mixture was added to S_{mix}. Then the whole mixture was diluted with water to develop nanoemulsion. Nanoemulsion can be developed by any of the two methods.

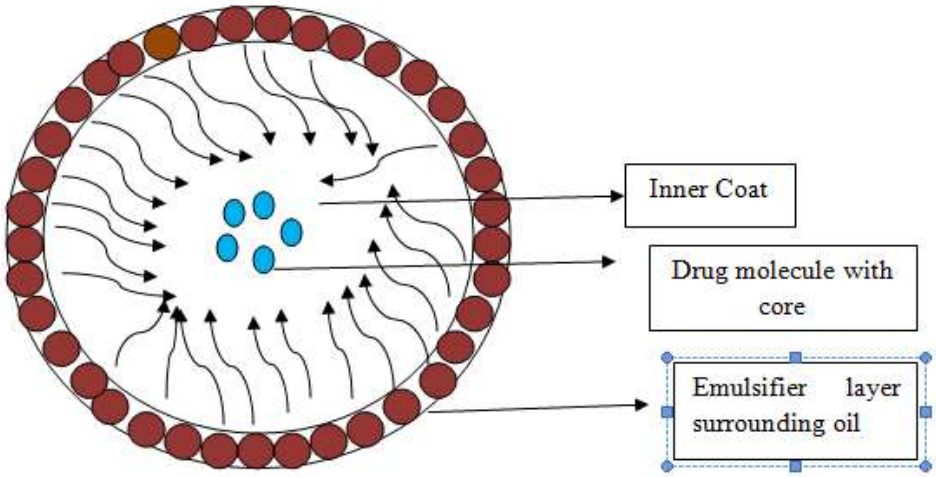


Fig 3: Diagrammatic Representation of Stabilised Nanoemulsion[43]

- **High Energy Emulsification Method (HEEM):** The nanosize of the droplets in the aqueous phase is a result of destruction of oil phase under standard conditions of time, and temperature using ultrasonicators that produce high shear force, high pressure homogenizers, and microfluidizers etc to decrease the particle size of internal phase to nano size [65]. Hence, this method utilizes external energy to develop a thermodynamically stable formulation. This method offers advantages such as the particle size of dispersed phase globules can be as small as 1nm by altering the excipients. Therefore this method is not applicable for thermolabile ingredients [66].

- **Low Energy Emulsification Method (LEEM):** This is a spontaneous and phase inversion method. LEEM is advantageous over HEEM since a more thermodynamically stable emulsion is obtained. Miscibility of the three components i.e., lipid, S_{mix} and water in a definite concentration results in a nanoemulsion instantly. Nanoemulsion can also be prepared alternatively by adding aqueous phase with or without surfactant [67]. The so formed NE contains dispersed nano sized droplets in continuous phase. The emulsification method is affected by the sequence of addition of the ingredients, pH, and properties of surfactant and co-surfactant [68]. LEEM is applicable for those surfactants whose HLB changes depending on temperature. Ex: Non ionic surfactants mostly polyethoxylated surfactants such as Cremophor EL, Labrasol, Tween 80, Tween 60, Tween 20, etc. Nanoemulgel prepared by incorporating hydrogel matrix in Nanoemulsion is affecting the pharmacokinetics of the drug. Especially hydrophobic drugs which have poor aqueous solubility are solubilised in the lipid phase before formulation of nanoemulsion [69].

4.2. Transformation of Nanoemulsion to Nanoemulgel.

The so formed nanoemulsion was converted into a nanoemulgel by adding the nanoemulsion to the gel base such as Carbopol 934, Carbopol 940, Carbopol 971, Polaxomer 407. The gel base may be naturally occurring such as Chitosan. Inclusion of nanoemulsion into the gelling agent affects the pharmacokinetics of the drug[70].

Selection of Gelling agent:
The gelling agent was selected based on

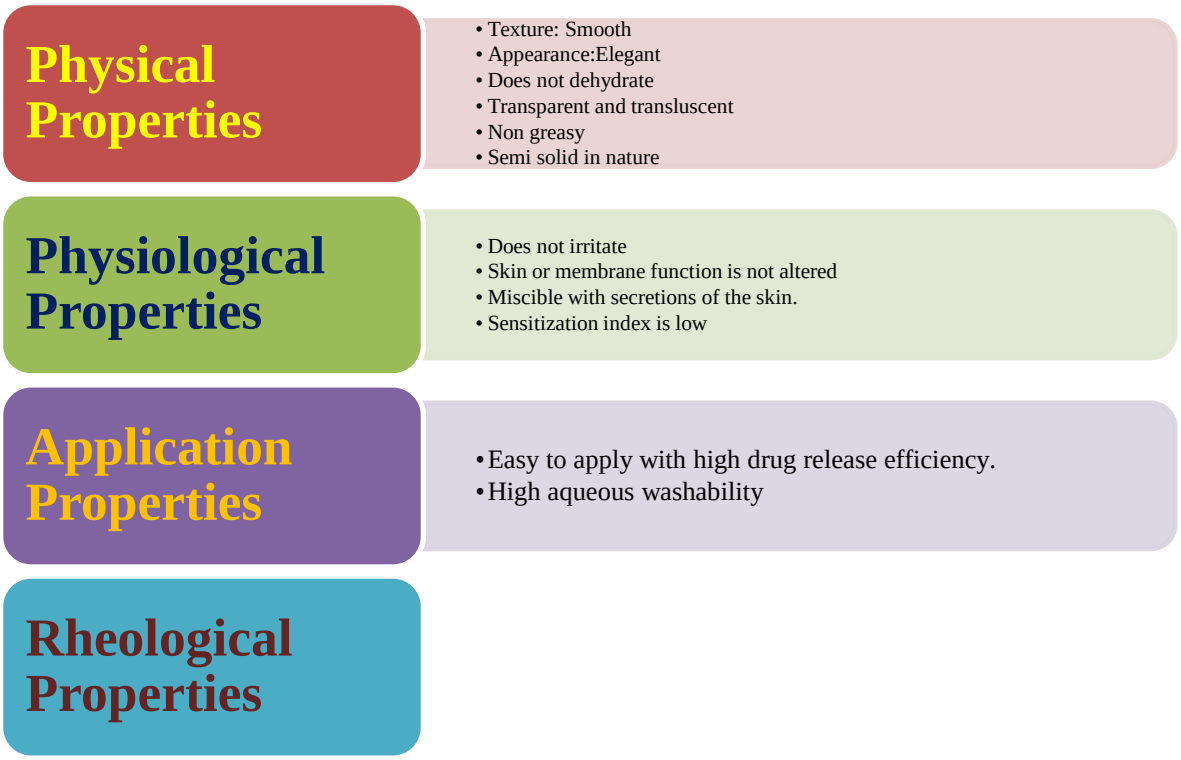


Fig 4: Factors to be considered while selecting a gelling agent[71].

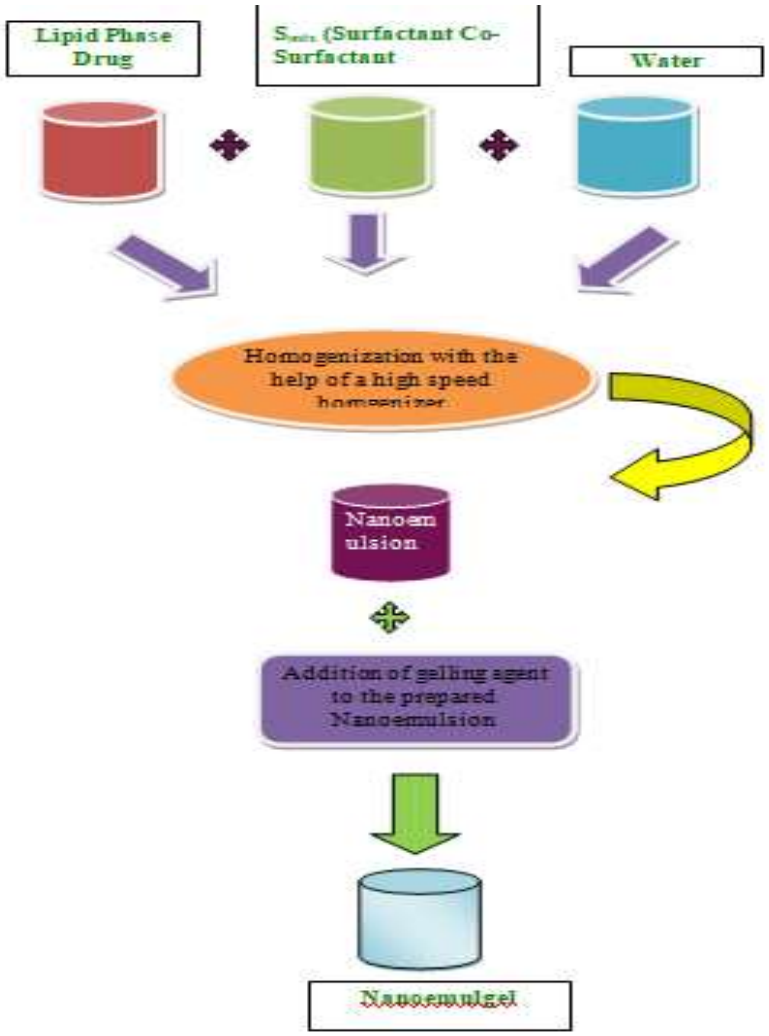


Fig 5: Steps involved in development of nanoemulgel.[1]

Recently, Dasgupta et al prepared and optimised Lirnoxicam nanoemulgel. They followed a different preparative method i.e. firstly screening of oil was done, and then added the screened oil i.e., Labrafac to the gelling agent containing dispersed phase accompanied by neutralizing the gel on addition of triethanol amine. Then the optimised surfactant Tween 80 and co-surfactant Plutonic F 68 are incorporated into the oil and gel mixture. Therefore, nanoemulsion gel was obtained by addition of water. The resultant nanoemulgel has neutral pH of 6-7 which is perfectly suitable for cutaneous absorption of drug. The pharmacodynamic studies proved that the duo of nanoemulsion and nanoemulgel are superior in treatment of Edema. In vitro studies and permeation flux through skin were greater in the duo of nanoemulsion and nanoemulgel than in marketed gel [72].

Pund and her team described nanoemulgel as a potential carrier of drug to treat Psoriatic arthritis and melanoma of the skin. They conducted ex-vivo studies of the formulation on rats skin to encounter its permeability transdermally. They observed that the formulation development does not have any effects on normal cell but is toxic towards specific cells i.e. human melanoma cell. They developed the preparation in such a manner that the transdermal delivery of drug is specific to affected cells. Therefore, such a formulation is said to contain less dose of the drug producing optimum side effects and is economical. Though the rat's skin was exposed to nanoemulsion for about 12 hours there was no alternation in the physiology of the skin but was observed in the pathological sections. The positive control group that was given nitric oxide showed distinguished changes in the epithelium when compared to negative control. A-375 and SKMEL -2 were used to study the antiproliferative activity in the test cells by activating transcriptional activity [55].

Similarly, Nystatin nanoemulgel used for mycological cure showed greater drug release than solid dispersion or marketed cream [73]. Sampathi et al prepared nanoemulgel of Itraconazole. Firstly, nanoemulsion was prepared using ultrasonification by dissolving drug in oil phase i.e. Eugenol and heated along with lecithin and sodium chlorate as surface active agent, Carbopol 934 is accustomed as gel base to convert into nanoemulgel and triethylamine was used to adjust the pH. In this study 0.1% limonene was used to mask the odour and also a permeation enhancer. Itraconazole nanoemulsion containing hydrogel base showed enhanced drug release in vitro and penetration into the skin. Thus nanoemulgel was prepared to release the drug for a prolonged time to reduce the dosing frequency [28].

Mirza and their team also used Itraconazole as the model drug to develop nanoemulgel. They used tea tree oil as lipid phase, Tween 20, Labrasol and Carbopol 934 as surface active agent, co-surfactant and gelling polymer correspondingly. They studied that inspite of same polymer concentration, improved permeability and higher flux of the active ingredient is accomplished with nanoemulgel than conventional gel. The tea tree oil used as lipid phase poses anti-microbial activity and therefore the preparation showed synergistic anti-microbial effect[74].

The epidermis of the skin acts as a protective layer and prevents the entry of harmful substances. The penetration of high molecular weight drugs i.e. greater than 500 Daltons and lyophobic is limited through cell membrane. Therefore, large molecular size and limitations associated with oral administration such as low water solubility, reduced permeability and acidic degradation of Amphotericin B recommended developing it into a parenteral dosage form. Furthermore, it helps to overcome the said limitations and side effects such as nephrotoxicity [75]. Hussian et al came forward with a novel formulation which is given by topical route. This formulation is said to show antifungal activity and also avoid systemic difficulties caused by the drug. The investigators formulated Amphotericin B nanoemulgel by incorporating prepared nanoemulsion into a gelling agent Carbopol 980 succeeded by high speed homogenisation. Sefsol 218 and diethyl sulfoxide in ratio 1:1 is optimised as oil phase. Triethylamine and gelling agent were mixed and left over night to remove air and cross link the gel base with triethanolamine. The in vitro dissolution studies of drug, diffusion through skin and rupturing red blood cells were acceptable. Skin irritation test was performed using Wistar Albino rats. There was no evidence of Erythema or Edema when the formulation was applied at different time intervals. To study in vivo skin penetration and in vitro permeability a dye named Rhodamine 123 was added to nanoemulsion and nanoemulgel and observed for the diffusion of drug into the skin by means of Fluorescence Correlation Microscope[76]. The developed nanoemulsion and nanoemulgel of Amphotericin is having low viscosity, so the release of drug in the initial hours is slow on comparision to it' solution form. Sustained release of nanoemulsion showed zero order kinetics where as drug release from Amphotericin B solution followed first order kinetics. Comparatively, cumulative drug penetration was greater in nanoemulgel and nanoemulsion than a convention gel. The incorporation of surfactant and co-surfactant i.e. Tween 80 and Transcutol P has a synergistic effect on permeation of high molecular weight drugs transdermally. Therefore, study revealed that the formulation showed enhanced pharmacodynamic affect and in vitro anti-fungal activity. Topical delivery of Amphotericin was more effective than oral delivery [77].

Arora et al prepared Ketoprofen nanoemulgel by addition of Carbomer 940 as gelling agent to nanoemulsion. The lipid, surface active agent and co-surfactant were selected from solubility and transmittance values. The preparations were optimised for various characteristics such as thermal stability, percentage drug content, spreadibility, viscocity, and permeation characteristic of drug in ex vivo conditions [78]. Nanoemulgel of Ketoprofen had higher flux, lower lag time for permeation than marketed formulation and solution dosage form. In this study it was observed that amount of surfactant and co-surfactant are inversely proportional to the penetration ability i.e. on reducing from 75% to less than 35% the formulation showed better penetrability. This study proved that salvation of the skin layer containing alpha-keratin and the capability of Transcutol P to from hydrogen bond resulting in diffusion of drug through the skin[79].

Low energy emusification method was followed to develop Diclofenac Sodium microemulgel by incorporating Chitosan and polylysine, a cationic polymer. Yang and group evaluated the developed formulation and observed that the permeation of active ingredient via skin was increased by 1.56-5.76 times than commercially available emulgel and hydrogel

formulation of same drug. Furthermore, they studied that the prepared microemulgel has self preserving activity because of the presence of polylysine[80].

Delivery of the drug from nanoemulgel is not only restricted to the transdermal route but researchers has studied that they can also deliver the drug to treat periodontitis, vaginal infection, occular delivery and as a cosmetic.

Anayanti et al., prepared nanoemulgel with 4% of grape seed oil and 3.2% of anios triazine which is a chemical absorbent and possesses sun screen property as the liquid phase and carbapol 934 as gelling agent. Vitamin E contained in grape seed oil, acts an antioxidant for skin. They studied the sun protection factor and physical stability of nanoemulgel sunscreen were enhanced by addition of grape seed oil and anisotriazine as sunscreen material in same concentration in comparison to emulgel containing same concentration of sunscreen material[81].

Srivastava, and his team formulated nanoemulgel using Ketoprofen for the treatment of periodontitis. This nanoemulgel contain Eugenol as oil phase and Carbapol 934 and Polaxomer 407 as gel forming agents. They study reflected that an increase in concentration of Polaxomer 407, decreases the drug release from nanoemulgel. Pharmacodynamic evaluation reveals that the nanoemulgel was able to reduce gingival index, mobility of tooth and alevolar bone loss. The use of Eugenol as lipid phase showed additive effect of Ketoprofen to treat periodontitis[82].

Gurjot Kaur and her team studied that nanomaterial enhances the advantages of the active ingredient like minodoxil engineered through scalp.[83]

Nanoemulgel was proved as a challenging drug delivery system for ophthalmic preparations. Its gel like droplets can accommodate sufficient active ingredient and deliver it to the and aqueous humor parts cornea of eye [84].

Manami Dhibar et al formulated curcumin loaded in situ nanoemulgel for opthalmic delivery by using thermosensitive polymer Pluronic 127. They studied the nanoemulgel is unique to deliver curcumin to the eye for a prolonged period of time, to improve patient compliance, and to reduce number of doses by sustaining and prolonging the systemic absorption of curcumin[85].

Tayel and his co-workers developed Terbmatine nanoemulgel to cure ocular fungal infections. Miglyol 812 was used as lipid ingredient and Cremophor EL, PEG400, Gellan gum as surfactant, co-surfactant and gelling agent respectively. 0.5% of drug was incorporated. Nanoemulgel was produced by addition of aqueous gellan gum to the optimised nanoemulsion. Fluid electrolytes and proteins were cross linked with Gellan gum to produce in-situ gelation. Gamma radiation along with dry ice was used to sterilize optimized nanoemulgel. They performed pharmacokinetic studies on Rabbit and observed greater C_{max}, delayed T_{max} , delayed residence time and enhanced bioavailability [86].

Pathak and his team developed a nanoemulgel for ocular delivery of Fluconazole using Capmul MCM as lipid phase, homogenized with Tween 80 and Transcutol P and gelatinized with Carbopol 934. Therefore, it was observed that in vitro anti fungal activity was enhanced by 3.71 times in nanoemulgel of Fluconazole compared to the solution dosage form[87].

Nanotechnology has been playing a predominant role in formulation of Cosmetic preparations. Harwansh et al prepared nanoemulgel of Ferulic acid, which can absorb UV radiation and prevents damage to skin caused by UV radiation. The Nanoemulgel is developed by dispersing pre soaked gelling agent (Carbapol 930) into distilled water. Low pressure method was used to develop Nanoemulsion. Therefore a uniform dispersion of gel, and excipients such a PEG 400, propylene glycol, isopropyl alcohol, triethanolamine were homogenized to obtain a Nanoemulgel. The droplet size of formulation influences the in vitro permeability. Moreover, permeability and control release of Ferulic acid from the prepared nanoemulgel was effective against exposure to UV radiation on even after a period of 4 hours of application[88].

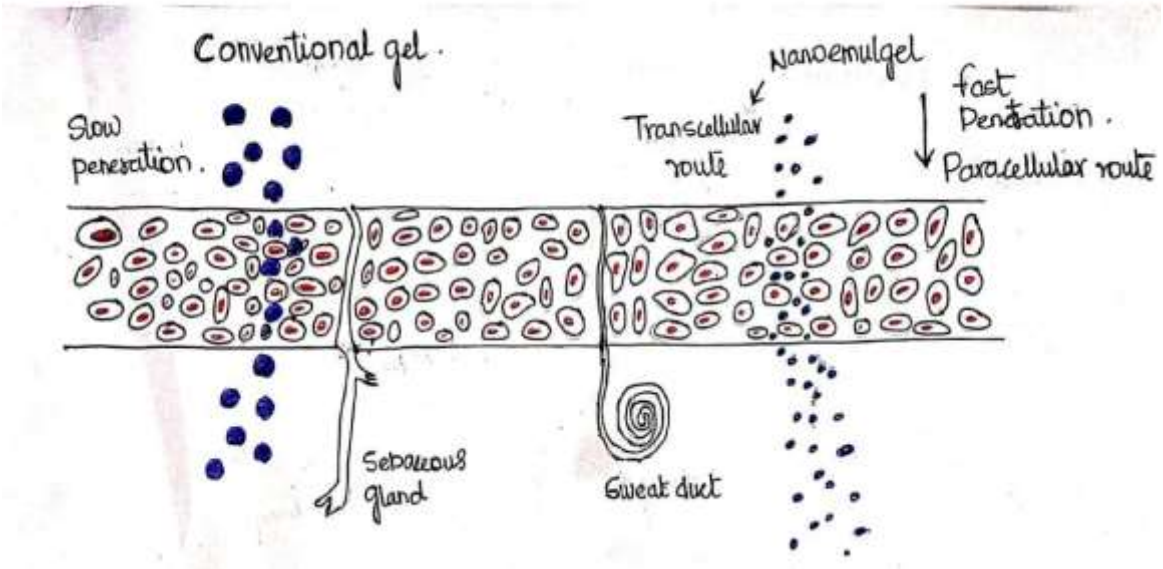


Fig 6: Diagrammatic representation of penetration of conventional gel and nanoemulgel through skin.[16]

Table 6:Lipid phase, Surfactant, Co-surfactant and Gelling agent used in various studies

S.No	Drug	Lipid Phase	Surfactant and Co-Surfactant	Gelling Agent
1.	Carbamazapine	Maisine	Tween 80 and Lauroglycol	Xanthan gum
2.	Celecoxib	Capmul 908P	Acconon and Capmul MCM	0.25-0.75% Carbopol-940
3.	Oxiconazole	Castor oil	Tween 80 and Propylene Glycol	Carbapol 934P
4.	Ketoconazole	Labrafac	Tween 80 and PEG 400	Carbapol 934 and Polaxomer 407
5.	Ketoprofen	Eugenol	Cremophore EL and Transcutol P	Carbapol 934 and Polaxomer 407
6.	Piroxicam	Oleic acid	Tween 80 and Ethanol	Carbopol 934
7.	Diclofenac	Mixture of clove oil and Iso propyl myristate	Tween 20 and PEG 400	Carbopol 980
8.	Snake head fish	Olive oil	Tween 80 and PEG 400	HPMC
9.	Aceclofenac	Oleic acid	Tween 20 and Ethanol	Carbapol 934
10.	Etoricoxib	Oleic acid	Tween 80 and Propylene Glycol	1.5% Carbopol 934
11.	Thymol	Caprylic acid and isopropyl myristate along with tea tree oil in the ratio 2:1:1.	Tween 20 and PEG 400	Carbopol 940
12.	Itraconazole	Eugenol	Lecithin and Sodium Cholate	3% Carbopol-934
13.	Tolnaftate	Almond oil	Tween 80 and Propylene Glycol	Carbopol 934
14.	Epirnomectin	Castor oil	Tween 80 and Ethanol	Carbomer 940
15.	Swietenia macrophylla	Swietenia macrophylla	Sucrose Laurate 1695, Oleate 1570 and Palmitate 1570	Carbopol 934 and 940
16.	Virgin coconut oil	Virgin coconut oil	Tween20, Span 20 and Polyethylene Glycol	Carbopol 934
17.	Leflunomide	Caproyl 90	Cremophor EL and Transcutol HP	Pluronic F127
18.	Fluconazole	Capmul MCM	Tween 80 and Transcutol	Carbopol 934P

5. CONCLUSION:

Nanoemulgel usually contains a lipid phase, surfactant, co-surfactant, and a gelling agent. The method of selection of required constituent and the amount of each constituent to be incorporated into the nanoemulgel requires a skilled knowledge. Furthermore, various manufacturing techniques affect the characteristics of final preparation.

Therefore, the development of thermodynamically stable nanoemulsion and its conversion into nanoemulgel is based on optimization of excipients and method of preparation. The studies revealed that conversion of nanoemulsion into a nanoemulgel i.e. nanoemulsion thickened with hydrogel, is more compatible and is more efficient than ordinary nanoemulsion meant for topical delivery. The viscosity of the nanoemulgel makes it more stable thermodynamically compared to a nanoemulsion because of the lowered surface tension and decrease in potency of the dispersed phase. Hence, a formulation with superior and prosperous transdermal penetration especially to deliver a lipophilic drug moiety with increased skin permeation delivering drug molecule into the the skin, increased exposure time, and deposition of a thin coating over the stratum corneum to prevent dehydration of the skin is prepared. Marketed nanoemulgels are trying to improve the beneficial aspects and investigational interest of this upcoming nanopreparation.

The formulation scientists in the pharmaceutical industry successfully incorporated the nanoemulsion in hydrogel which showed improved therapeutic efficiency in various pathophysiology conditions. Moreover it is user acceptable due to its non-greasy and gel like consistency with sustain release property on transdermal application. Nanoemulgel incorporated with active ingredient is used to treat bacteria, mycological, viral infections and even melanoma can be successfully cured. Therefore more molecular assessment of the drugs absorption process is necessary. Hence this emerging topical delivery system is under research to treat dermatological disorders and also improvise certain systemic ailments.

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