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A Review on Emulgel: Focus on Reported Research Works of Synthetic and Herbal Drugs

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Emulgel, Nanoemulgel, Emulsion, Herbal Extracts

ABSTRACT:

Introduction: Topical drug delivery refers to the administration of medications directly to the skin or mucous membranes for local therapeutic effects. This method is commonly used in dermatology, cosmetology, and certain medical conditions where localized treatment is required. Topical drug delivery offers several advantages, such as targeted action, reduced systemic side effects, and improved patient compliance, localized treatment, convenient and non-invasive action**.**

Objective: The use of emulgels, which are used for localised action, has suddenly increased in the modern society. The emulgels have the direct accessibility to the skin for the treatment of chronic diseases such as bacterial and fungal infections, acne, and psoriasis. Therefore, the current review focused on importance of emulgel in novel drug delivery systems.

Methods: The review specifies the composition, method of preparation, characterization, routes of administration, and applications of emulgel technologies.

Results: The commonly used gelling ingredient is Carbopol and various other excipients are also used in the formulation like aqueous material, oils, emulsifiers, penetration enhancers, preservatives and pH adjusting agent and were prepared in two steps, firstly, preparation of emulsion and gel base, followed by incorporation of emulsion into gel base. A nanoemulgel is also prepared in a similar manner that is by incorporating a prepared nanoemulsion into gel matrix. The emulgel formulation is characterized for physical characteristics, spreadability test, swelling index, pH, accelerated stability studies, drug content determination, extrudability study, bio adhesive strength and in-vitro & in-vivo drug release studies. Emulgels are prepared for various routes of administration like topical, ocular, nasal, vaginal and oral. The current review presents a concise list of works that have been reported on formulation of emulgel using synthetic drugs and herbal extracts. The review also focused on the reports of clinical works.

Conclusions: The emulgel formulations can be easily recognized as the better novel drug delivery system technologies because of easy preparation, stability and technology development.

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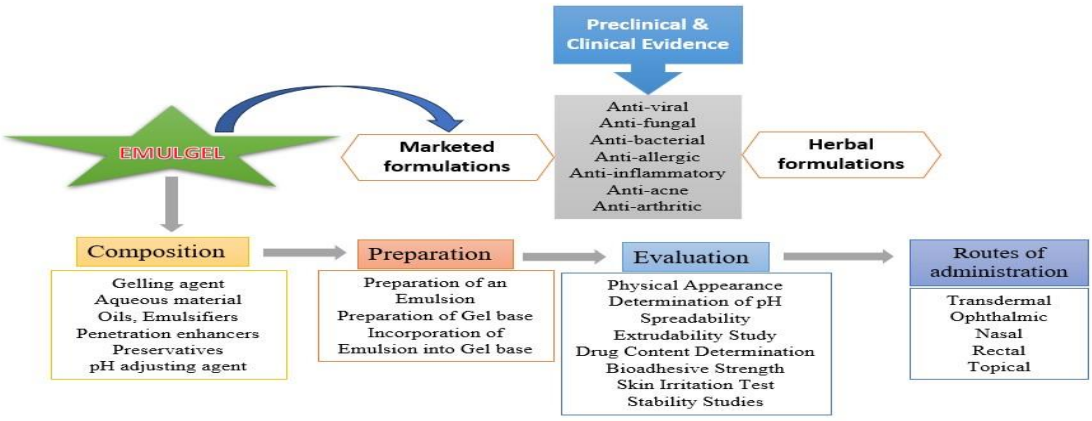

Graphical Abstract

INTRODUCTION

Topical drug delivery implies the application of a drug-containing formulation to treat the skin infection on the surface of the skin directly. Gel formulations typically offer faster medication release than traditional ointments and lotions. Topical channels such as the skin, rectal, vaginal, and ophthalmic are utilised to deliver drugs for localised action on the body. Emulgels are created to overcome the fundamental constraint of gels, which is the difficulty in delivering hydrophobic medications [1]. Emulgels are emulsions of the oil-in-water or water-in-oil variety that have been combined with a gelling agent to form a gel. The most reliable and effective delivery system for hydrophobic or poorly water-soluble medicines is emulsified gel [2]. In simple terms, emulgels are the fusion of an emulsion and a gel. Emulgel are typically utilised when other drug delivery methods fall short in their ability to effectively treat the skin conditions such as bacterial and fungal infections, acne, psoriasis, etc [3].

The novel polymers act as emulsifiers and thickeners in the emulgel formulation because to produce gelling ability and additionally makes it possible to produce stable emulsions and creams by reducing surface and interfacial tension and increasing the aqueous phase viscosity of the formulation. Emollient, non-staining, thixotropic, readily spreadable, easily removed, greaseless are the properties that are beneficial for the dermatological treatment and also includes a longer shelf life, bio-friendliness and a clear appearance [4].

Emulgel is the combination of two parts. Firstly, the type of dispersion which is a two-phase system called an emulsion, in where an immiscible liquid is mixed with another liquid. In order to stabilize the system, when the formulation becomes unstable, emulsifying compounds must be added. Emulsions, which are used to carry drugs, are available in o/w and w/o varieties. They have high skin penetration and are easily removed from skin. Second, the gel is the physical condition that possesses characteristics that fall between the solids and liquids. A gel is made of a polymer that expands when fluid is present and may even do so internally. The volume of fluid that the gel can hold determines how rigid it is. These gels have the texture of a solid material but are moist and squishy. These have the ability to modify their own physical composition drastically, going from solid to liquid [5].

Rationale of Emulgel

Topical medications including ointments, creams, and lotions are frequently used yet have significant drawbacks. When administered, they are extremely sticky and make the patient uncomfortable for several reasons. Additionally, they display the stability issue, have a lower spreading coefficient, and need rubbing when applying, which may result in dermatitis. The usage of transparent gels has increased in both pharmaceutical and cosmetic preparations as a result of all these aspects within the main group of semisolid preparations. Since many years ago, a gel has been used to transport painkillers and antibiotics to an injured area of the body. A gel is a colloidal dispersion that is

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typically 99% liquid by weight and is immobilized when it is applied to the skin by surface tension [6].

FORMULATION OF EMULGEL

Emulgel is made by combining a number of ingredients, some of which are listed below Table 1, in which the constituents are combined in specific formula to form an emulsion are aqueous material, oils, emulsifiers, gelling agents, penetration enhancers, preservatives and pH adjusting agent [7].

Table 1. Composition of Emulgel formulation

Constituents	Purpose	Examples	Reference
Aqueous material	Develops the aqueous phase, where the drug is dissolved along with it.	Purified water, alcohols	[8]
Oils	Forms the oily phase in the emulsion	Clove oil, Mentha Oil, Light Liquid Paraffin	[9]
Emulsifiers	Acts as a stabilizer for emulsions, and used to control emulsification process and also preventing liquids that normally don't mix from separating	Span 20, Span 80, Tween 20, Tween 80, Capmul 908, Span 60,	[10]
Gelling agents	Converts the liquid media into semisolid form and increase the viscosity of a liquid without changing its other properties.	Carbopol 934/940, HPMC K4M, HPMC, Xanthan Gum, Gelatin	[11]
Penetration enhancers	Enhances the transdermal drug delivery that through the skin helps to decrease the barrier resistance.	Propylene glycol, Cetyl alcohol, Polyethylene glycol	[12]
Preservatives	To prevent the microbial growth and extends the shelf life of the products.	Propyl Paraben, Methyl Paraben	[13]
pH adjusting agent	To achieve desirable pH for the formulation	Triethanolamine	[14]

PREPARATION OF EMULGEL

The emulgel formulation is prepared by the three specific steps that are:

Preparation of an Emulsion

The oil phase of the emulsion is prepared by dissolving emulsifier in the vehicle (oil). The aqueous phase of the emulsion is prepared by dissolving emulsifier in the vehicle (aqueous material). Depending on whether the drug is hydrophobic or hydrophilic, it is either dissolved in an ethanol solution or combined with an aqueous or oil phase of an emulsion. Then the preservatives are dissolved in the aqueous phase of emulsion with the addition of penetration enhancer. Each phase's temperature is individually increased to be between 70°C and 80°C. The oily phase was then added to the aqueous phase and constantly agitated as it cooled to room temperature.

Preparation of Gel base

The gelling agent is dissolved in purified water while being constantly stirred at a moderate speed. Triethanolamine (TEA) is subsequently utilized to bring the pH level between 6 to 6.5.

Incorporation of Emulsion into Gel base

In a 1:1 ratio, the emulsion and gel base are combined with the addition of glutaraldehyde, which functions as a cross-linking agent.

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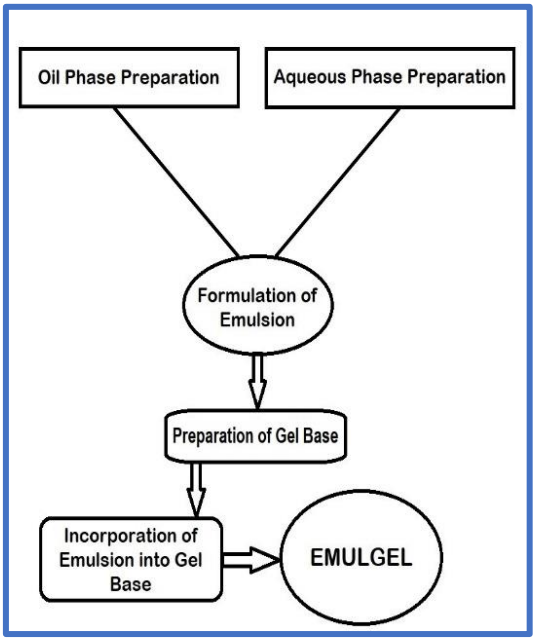

Figure 1. Steps involved in preparation of an Emulgel

PREPARATION OF NANOEMULGEL

The nanoemulgel formulation is prepared by two steps that are:

Preparation of Nano emulsion

To develop the nano emulsion, initially non-aqueous phase was formed by combining the drug in 1 ml of ethanol using an ultrasonic bath dissolving in castor oil in a 40°C water bath. The mixture was subsequently transferred into a round bottom flask of the appropriate size and fixed on rotary evaporation at 38°C for 20 minutes to remove the ethanol. Aqueous phase in a specific volume has been produced. To develop the primary emulsion, it is constantly agitated on a magnetic stirrer, the aqueous phase was progressively introduced to the non-aqueous phase. In order to produce the final nano emulsion, this original emulsion undergone three cycles of high-pressure homogenization at 350 bars.

Preparation of Nano emulgel

In order to develop the hydrogel matrix for the nanoemulgel, a gelling agent was soaked in water. After that, a gradual, continuous stirring process was used to add a drug nanoemulsion to the gel matrix. By bringing the pH level to 6-7 and adding aqueous solution, the desired nanoemulgel was produced [15].

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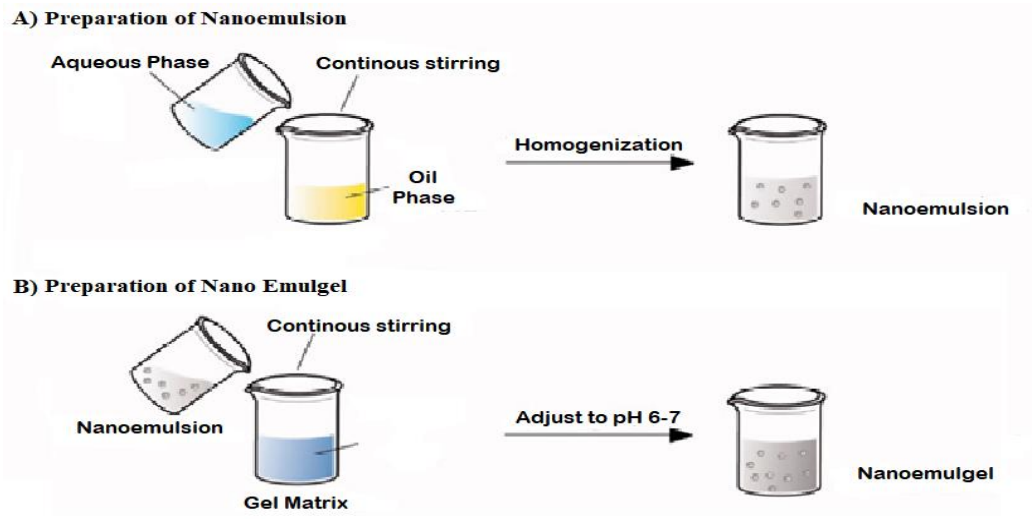

Figure 2. Nanoemulgel Preparation

EVALUATION OF EMULGEL

There are several evaluation techniques involved, for the analysis and assessment of the emulgel formulation that are:

Physical Appearance

The visual characteristics of the prepared emulsion formulations—color, homogeneity, consistency, and phase separation are checked [16].

Determination of pH

A pH meter is utilized to determine the pH levels of 1% aqueous solutions of the produced formulation. pH is measured after fully submerging the electrodes in the semisolid mixtures [17].

Spreadability

The apparatus suggested by Mutimer et al [18] is adapted appropriately in the lab and used for the investigation to measure spreadability. It consists of a wooden block with a pulley attached to one end. The 'Slip' and 'Drag' characteristics of emulgels are utilized in this method to assess spreadability. A ground glass slide is fixed to this block. Extra emulgel (around 2 gm) is being examined on this ground slide. Then, an additional glass slide with a hook and a fixed ground slide dimension is emulgel sandwiched between the both slides. A 1 kg weight is placed on top of the two slides for five minutes in order to eliminate air and generate a uniform emulgel layer between them. Extra emulgel is scraped off the edges. The top plate is then subjected to an 80gm pull. Record the time (in seconds) required for the top slide to travel 7.5 cm using a thread that is attached to the hook. Better spreadability is indicated by a shorter interval. Spreadability was calculated by using the formula:

$$S = M \times L/T$$

where,

S = spreadability,

M = Weight tied to upper slide,

L = Length of glass slides,

T = Time taken to separate the slides completely from each other.

Swelling index

A 50 ml beaker with 10 ml of 0.1 N NaOH and porous aluminium foil is used to hold one gram of emulgel. The samples are then removed and reweighed at various intervals [19]. Swelling index is determined by the equation;

$$\text{Swelling index (SW) \%} = [(Wt-Wo)/Wo] \times 100$$

where,

Wt = Weight of swollen emulgel after time t,

Wo = Original weight of emulgel at zero time.

Extrudability Study

An empirical test is often carried out to establish the amount of force necessary to extrude the material from the tube. a technique for calculating the amount of applied shear at the point on the rheogram where plug

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flow happens when the yield value is exceeded. The method used in the current study to assess the extrudability of an emulgel formulation was based on the volume of emulgel and the emulgel extruded from a lacquered aluminium collapsible tube on application of the weight in grams required to extrude at least 0.5 cm of emulgel ribbon in 10 seconds. Greater extrusion volume increases extrudability. Each formulation's extrudability is measured three times, and the average values are given [20]. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (gm) /Area (cm^2)

Drug Content Determination

Take 1 gram of emulgel. Add a suitable solvent to it to combine it. To create a clear solution, filter it. To gauge the material's absorbance, use a UV spectrophotometer. The same solvent is used to prepare the standard drug plot. By including the absorbance value in the standard plot, concentration and drug content may be calculated [21].

Drug Content = (Concentration × Dilution Factor × Volume taken) × (Conversion factor)

Bioadhesive Strength Measurement

The modified method is used to measure the bioadhesive strength. After being divided into pieces, the new skin is cleaned with 0.1 N NaOH. Two glass slides, one of which was connected to the wooden piece and the other to the balance on the right side, were each connected to two skin parts. We added weight to the left-hand pan to balance the right and left pans. One gram of topical emulgel is sandwiched between the two slides containing the hairless skin sections after the extra weight in the left pan has been removed and pressure is used to push any air bubbles out of the way. For five minutes, the balance is held in this posture. At a rate of 200 mg/min, weight is gradually added until the patch separates off the skin's surface, using the left-hand pan. The weight (in grams) necessary to remove the emulgel from the skin's surface served as a gauge for the bioadhesive strength [22]. The bioadhesive strength is calculated by using following:

Bioadhesive strength = Weight required (in gms) /Area (cm^2)

Skin Irritation Test

The test for skin irritability was conducted on mice. The mice were monitored for 24-hour after administering the emulgel. Skin redness or changes in the morphology of the skin were not listed as signs of skin irritation in the formulation. The formulation is therefore found to be safe for topical application and unlikely to result in skin irritation [23].

Stability Studies

The prepared emulgel formulations were stored for three months at 4°C, 25°C and 40°C, in collapsible tubes away from the light. The physical properties, rheological behaviour, pH, skin sensitivity test, drug release studies and microbiological testing of the samples are assessed after storage. [24].

Routes of Drug Administration of Emulgel:

The choice of the route of drug administration depends on the site of application and the desired therapeutic effect. The most common routes of drug administration of emulgel are as follows:

Transdermal route

Some drugs can be formulated in emulgels to facilitate their transdermal absorption. Transdermal emulgels allow the drug to penetrate through the skin and enter the bloodstream, providing systemic effects. This route is often used when a controlled and sustained release of the drug is desired.

Ophthalmic route

Emulgels can be used for ophthalmic drug delivery, where they are applied to the eye surface. This route is utilized for treating eye infections, inflammation, and other ocular disorders.

Nasal route

Emulgels can be used intranasally for delivering drugs through the nasal mucosa. This route is useful for drugs that require rapid absorption or for targeting the central nervous system through the blood-brain barrier.

Rectal route

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Emulgels can also be formulated for rectal administration, where the drug is applied to the rectal mucosa for local or systemic effects.

Topical route

Emulgels are primarily used as topical formulations, applied directly to the skin for localized effects. They are commonly used for various dermatological conditions such as skin infections, inflammation, and pain relief. The epidermis and dermis are the two important skin layers. In the subcutaneous layer beneath the skin, there are numerous blood vessels. Intercellular, transcellular, and follicular drug absorption through the skin are the three main processes.

Most medications travel over the tortuous route to the viable layers of the skin that avoids corneocytes and passes via the lipid bilayer. Since many years ago, antimicrobial medications and painkillers have been delivered to an affected region of the body with skin-rubbed lotions and gels. Among these are creams to relieve arthritis pain, topical creams for skin diseases, and gels and creams for vaginal yeast infections. Other medications can now be absorbed through the skin thanks to new technologies. These can be used to treat the entire body in addition to the skin's afflicted areas. These can be used on hairy skin without the discomfort other topical formulations may cause. It's important to note that not all drugs are suitable for formulation as emulgels, and the choice of route depends on the specific drug, its intended therapeutic effect, and the patient's condition. Additionally, the use of emulgels should be done under the guidance and prescription of a qualified healthcare professional to ensure safe and effective drug administration [25].

MARKETED FORMULATIONS

There various marketed emulgel formulations available for various disease conditions, they may anti-bacterial, fungal, acne or NSAIDs [26] are mentioned in below Table 2.

Table 2. Marketed Formulations

Brand Name	Active Ingredient	Manufacturer	Uses
Voltarol 1.16% emulgel	Diclofenac Diethyl ammonium salt	Novartis	Anti-inflammatory
Miconaz H emulgel	Miconazole nitrate & Hydrocortisone	Medical Union Pharmaceuticals	Antifungal
Denacine Emulgel	Clindamycin phosphate	Beit Jala Pharmaceutical Company	Anti-acne
Diclon emulgel	Diclofenac diethylamine	Med Pharma	Anti-inflammatory
Cataflam emulgel	Diclofenac potassium	Novartis	Anti-inflammatory
Voveran emulgel	Diclofenac diethylamine	Dr Reddy’s Laboratories Ltd	Anti-inflammatory
Lupigyl gel	Metronidazole, Clindamycin	Lupin Pharma	Antibacterial
Avindo 2% gel	Azithromycin	Adcock Ingram Healthcare Pvt. Ltd	Antibacterial

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Cloben gel	Clotrimazole, Beclomethasone	Indoco Remedies	Antifungal
Acent gel	Aceclofenac	Intra Labs India Pvt. Ltd	Anti-inflammatory
Topinate gel	Clobetasol propionate	Systopic Pharma	Anti-inflammatory
Pernox gel	Benzoyl peroxide	Cosme Remedies Ltd.	Anti-acne
Isofen Emulgel	Ibuprofen	Beit Jala Pharmaceutical Company	Anti-inflammatory
Dosanac Emulgel	Diclofenac diethyl ammonium	Siam Bheasach	Anti-inflammatory
Excex gel	Clindamycin, Adapalene	Zee Laboratories Ltd	Anti-acne

PAST WORK DEVELOPMENT & CLINICAL WORK

There are various research and developmental work on emulgel formulations have been reported, in which the few APIs are enlisted in below Table 3.

Table 3. APIs reported for emulgel formulations

Drug	Category	Route Of Administration	Result	Reference
Acyclovir	Anti-viral	Topical (Emulgel)	Proved the drug permeation into the skin.	[27]
Atorvastatin	Anti-fungal	Vaginal (Emulgel)	Showed the antifungal activity against C. albicans.	[28]
Betamethasone & Levofloxacin	Anti-bacterial	Ophthalmic (Emulgel)	Showed good stability as compared to other formulations and commercial eye drops.	[29]
Chlorphenesin	Anti-fungal	Topical (Emulgel)	Showed good antifungal activity.	[30]
Ciprofloxacin	Anti-bacterial	Topical (Emulgel)	Showed good anti-microbial activity compared to commercially available gel.	[31]
Clarithromycin	Anti-microbial	Topical (Emulgel)	Showed good antimicrobial activity when compared to the marketed Azithromycin gel.	[32]
Coenzyme Q10	Anti-ageing	Topical (Emulgel)	Increases the density of collagen and the quantity of fibroblast cells in UV radiation skin-aged induced-mice, reflecting its potential to reverse the aging process of the skin.	[33]
Dasatinib	Wound healing	Topical (Emulgel)	The hydration layer is developed, which encourages skin lipid swelling and enhances permeability.	[34]

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Ebastine	Anti-allergic	Topical (Emulgel)	After 12 hours, the improved formulation released 74.25 ± 1.8% of ebastine. Histamine-induced allergy in rabbits has anti-allergic behaviour is observed.	[35]
Itraconazole & Clotrimazole	Anti-fungal	Topical (Emulgel)	Showed good antifungal activity against S. brasiliensis yeasts.	[36]
Ketoconazole	Anti-fungal	Topical (Emulgel)	Showed good anti-inflammatory activity due to lack of excessive oily bases.	[37]
Ketoprofen	Anti-inflammatory	Topical (Emulgel)	Exhibited enhanced anti-inflammatory activity in comparison to gel that is available for commercially.	[38]
Mefenamic acid	Anti-inflammatory	Topical (Emulgel)	Showed superior analgesic and anti-inflammatory effects in comparison to commercial diclofenac sodium gel.	[39]
Meloxicam	Analgesic	Topical (Emulgel)	Showed good stability and showcased an alternative to the long-term usage of analgesics for relieving the symptoms of knee osteoarthritis.	[40]
Methoxsalen	Psoriasis	Topical (Nano Emulgel)	Showed better activity when compared with marketed plain gel.	[41]
Metronidazole & Niacinamide	Antibacterial	Topical (Emulgel)	To minimize facial redness, just a slight attenuation effect was produced.	[42]
Minocycline	Anti-acne	Topical (Nano Emulgel)	Showed better anti-inflammatory activity.	[43]
Mupirocin	Anti-bacterial	Topical (Emulgel)	Showed good stability and anti-bacterial effect, when compared with marketed formulation against Staphylococcus aureus.	[44]
Naproxen & Eugenol	Anti-inflammatory	Topical (Emulgel)	naproxen and eugenol combinedly showed their analgesic and anti-inflammatory properties.	[45]
Piroxicam	Anti-arthritic	Topical (Emulgel)	Showed stronger anti-inflammatory effectiveness than the commercially available product.	[46]
Tretinoin	Anti-acne	Topical (Emulgel)	Superior anti-inflammatory activity	[47]

Acyclovir:

To enhance the topical delivery, the emulgel was designed using microsponges loaded with acyclovir. The drug release profile, drug loading efficiency, drug/polymer ratio, particle size, yield, PVA concentration and entrapment efficiency were all considered as critical product attributes. The study's results showed a considerable improvement in the drug's ability to pass when compared to a commercial formulation [27].

Atorvastatin:

The atorvastatin emulgel was formulated to treat mycoses. The formulation was optimized and evaluated the lowest inhibitory concentration against azole-resistant Candida albicans and its mechanisms of action

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by in vitro experiments to ascertain the antifungal activity of atorvastatin. The results showed that atorvastatin minimal inhibitory concentration against C. albicans. The study suggests that it is possible to assert that atorvastatin may be promising for drug repositioning towards the treatment of these opportunistic mycoses [28].

Betamethasone & Levofloxacin:

The ophthalmic emulgel was formulated that to deliver two drugs Betamethasone sodium phosphate and Levofloxacin which enables the simultaneous administration and prolonged release of the two medications, potentially increasing patient compliance and treatment adherence while extending the two medications' duration in ocular tissues. Therefore, the formulations' physical characteristics, viscosity studies, pH levels, drug assay, and in-vitro drug release studies were studied. The results demonstrated that the two pharmaceutical drugs were successfully released over a longer period of time [29].

Chlorphenesin:

By employing a 2^3-factorial design to examine the effects, regarding the drug release from the developed emulgels using two different types of gelling agents. The formulation's stability, drug release, physical characteristics, rheological behaviour and antifungal activity were all evaluated. For comparison, a topical chlorphenesin powder that is available commercially was utilized. The formulation exhibited greater drug release and anti-fungal properties than chlorphenesin powder and remained unchanged upon storage for 3 months [30].

Ciprofloxacin:

The ciprofloxacin emulgel was formulated to treat the local skin disorders. The formulations' physical studies, spreadability tests, pH levels, rheological research, in-vitro release studies, skin irritation test, drug assay determination and accelerated stability studies were evaluated for the formulations. The results showed that they were stable at different temperatures. Studies show that the viscosity of the employed polymer affects the drug's release [31].

Clarithromycin:

The clarithromycin emulgel was developed to treat localized skin conditions. The formulation was assessed to evaluate its stability tests, viscosity studies, antimicrobial activity, extrudability test, spreadability test, physical properties, pH levels, in-vitro & ex-vivo drug release studies. The formulation's results showed better activity and were satisfactory. When compared to commercially available azithromycin gel had shown comparable antibacterial efficacy. [32].

Co-enzyme Q10:

The Co-enzyme Q10 emulgel was developed to enhance CoQ10's stability and skin absorption since it comprises of protransfersome. According to an in-vivo drug release study, Protransf-CoQ10 emulgel successfully increased the collagen density and number of fibroblast cells in UV radiation skin-aged induced-mice, reflecting its potential to reverse the skin-ageing process and successfully boosted the stability and anti-ageing efficacy [33].

Dasatinib:

To minimize the systemic side effects, dasatinib was developed as a topical emulgel for the treatment of rheumatoid arthritis. The hot emulsification method was used to produce the emulgel, and the homogenization process was utilized to decrease the particle size. The formulation was assessed particle size determination, % entrapment efficiency, in-vitro drug release profile, ex-vivo skin permeation and in-vivo data analysis. The arthritis model demonstrated that the developed preparation might work well as an alternate therapy for rheumatoid arthritis [34].

Ebastine:

The ebastine emulgel was developed to study the physical characteristics, viscosity, pH, drug content, thermal analytical studies, spreadability factor, in-vitro drug release & in-vivo anti-allergic activity. The improved formulation significantly outperformed the brand-name drug Benadryl® in terms of in vivo anti-allergic action. This study found that a topical drug administration of ebastine-loaded emulgel for the treatment of urticaria/hives could be well tolerate and safe [35].

Itraconazole & Clotrimazole:

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Itraconazole and clotrimazole were incorporated in the formulation to produce an emulgel for the treatment of sporotrichosis against the yeast Sporothrix brasiliensis. The formulation's zeta potential, viscosity, in-vitro antifungal activity, and stability under various storage conditions were formulated & assessed. The results show the promising physicochemical characteristics and good in-vitro inhibitory activity against S. brasiliensis yeasts [36].

Ketoconazole:

The ketoconazole emulgel was developed to investigate the emulgel's potential as to improve the topical distribution. The formulations were assessed, based on their globule size, stability, viscosity, drug release activity, physical attractiveness, skin irritancy test and anti-fungal activity. In comparison, the commercially available ketoconazole cream had acceptable physical characteristics. It resulted in improved antifungal activity and drug release activity shown to be greater in formulation. The formulation remained unaltered for three months [37].

Ketoprofen:

Two different gelling agents were used to formulate the Ketoprofen emulgel. The formulation's anti-inflammatory efficacy was evaluated. In comparison to commercially available gel, all formulations demonstrated enhanced ketoprofen penetration and anti-inflammatory effectiveness. Therefore, in the topical emulgel, while avoiding GIT adverse effects, enhanced the uptake of ketoprofen and possessed potent anti-inflammatory capabilities. [38].

Mefenamic acid:

Mefenamic acid emulgel was developed to evaluate its anti-inflammatory properties. Rheology tests, spreading coefficient studies, bio adhesion strength, skin irritation studies, in-vitro release & ex-vivo release studies, anti-inflammatory activity research, and analgesic activity studies were performed. When compared to commercially available diclofenac sodium gel, the formulations displayed equivalent analgesic and anti-inflammatory effects [39].

Meloxicam:

The meloxicam emulgel was formulated for the management of pain and inflammation allied with osteoarthritis. The emulgel was fabricated by ultrasonication and micro fluidization method and also was optimized with centrifugation, heating-cooling cycles and transmittance parameters in addition to scale-up feasibility. The nanoemulsion was assessed for pH, rheology, textural properties, assay, accelerated stability study, in-vitro drug release study. Meloxicam emulgel showcased an alternative to the long-term usage of analgesics for relieving the symptoms of knee osteoarthritis [40].

Methoxsalen:

Methoxsalen emulgel was developed to improve anti-psoriatic action and epidermal localisation, using synthetic methoxsalen and natural babchi oil. The spreadability test, pH levels, viscosity studies, drug content assay, ex-vivo skin penetration and in-vivo investigations of the formulations were assessed. In comparison with normal gel, the nanoemulgels produced better effects throughout the skin [41].

Metronidazole & Niacinamide:

An emulgel was developed in order to release the active pharmaceutical ingredients (APIs) metronidazole and niacinamide, for the treatment of rosacea. The emulgel was also tested for API release in vitro, attenuated facial redness, mechanical stress-induced phase separation, studied for the impact of formulation variables on adhesion and viscosity. By comparing the designed emulgel to commercially available metronidazole products regarding API release, a realistic time range for drug delivery was offered in accordance with the predicted time of residence of the adhesive emulgel over the affected face area [42].

Minocycline:

The formulation and optimization of a nanoemulgel of minocycline facilitated better medication administration and increased drug retention in the area of application. The spreadability, viscosity, pH and physical texture studies were used to determine the morphological studies, size determination of droplets, viscosity studies, and refractive index of the nanoemulsion. The nanoemulgel demonstrated sustained-release behaviour.

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The recommended minocycline-containing nanoemulgel is anticipated to more effectively cure acne rosacea [43].

Mupirocin:

The topical delivery of mupirocin emulgel was developed to achieve the controlled release of mupirocin for the treatment of skin infection. Physical characterisation, ex-vivo & in-vitro drug release, antibacterial and anti-inflammatory study, UV, DSC spectra and FTIR were all performed; as a result, the development of stable controlled release of antimicrobial and anti-inflammatory activity was successful in the mupirocin emulgel [44].

Naproxen & Eugenol:

The naproxen-eugenol was formulation to fabricate and characterize the emulgel to increase the analgesic and anti-inflammatory effects, eradicate GIT adverse responses, and for transdermal drug delivery. These factors included physical properties, pH, thermodynamic stability studies, spreadability factor, extrudability and viscosity studies. According to the results of the experiments, naproxen and eugenol's anti-inflammatory and analgesic properties were enhanced when administered transdermally [45].

Piroxicam:

Compared to currently marketed pharmacological preparations, the piroxicam emulgel was developed to improve drug penetration through the skin. To examine the impact of independent factors, 3^2 full factorial designs were optimized. The produced formulation's appearance, typical globule size, drug content determination and in-vitro drug release were all assessed. The formulation displayed stronger anti-inflammatory effectiveness than the commercial product [46].

Tretinoin:

The Tretinoin emulgel was formulated to reduce the dose, control the release, and improve the stability by developing and optimizing tretinoin (TRT)-loaded topical emulgel formulation using 32 optimal response surface design (ORSD). The formulated TRT showed better spreadability and extrudability with spherical globules shape and showed significant anti acne activity against Propionibacterium acne and anti-inflammatory activity compare with Sotret® gel (a marketed product) without any signs of irritation and with more stability up to 3 months [47].

Clinical work

There are various clinical works reported on synthetic and herbal drugs used the topical route of administration for various chronic disease conditions [48]. The study and developmental works are enlisted in below Table 4.

Table 4. Clinical Works on Emulgel

Study	Study Type	Drug	Category	Route	Condition
Effect of Topical Diclofenac on Clinical Outcome in Breast Cancer Patients treated with Capecitabine	Phase 2 (Not recruiting)	Diclofenac & Capecitabine	Anti-inflammatory & Anti-cancer	Topical	Hand and Foot Syndrome
Voltaren Emulgel 2% Acute Ankle Sprain Non-Inferiority Study	Phase 3 (Complete)	Diclofenac diethylamine 2.32% gel, Diclofenac diethylamine 1.16% gel & Placebo	Anti-inflammatory	Topical	Pain
Fenugreek Wraps in Osteoarthritis of the Knee	Completed	Fenugreek Wrap & Diclofenac gel	Anti-arthritic	Topical	Osteoarthritis, Knee
Assess the Efficacy and	Phase 1	Ibuprofen,	Anti-inflammatory	Topical	Pain

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Safety in Volunteers of DCF100, TIB200 and SPR300 vs. Placebo and Control(s) in a UV Pain Model	(Complete)	Diclofenac, Methyl-salicylate / Menthol & Placebo			
Treatment of Chronic Anal Fissure	Terminated (Slow inclusion rate)	Levorag Emulgel & Diltiazem	Wound Healing	Topical	Chronic Anal Fissure
Topical Metformin emulgel vs Salicylic acid peeling in treatment of acne vulgaris	Phase 4 (Not yet recruiting)	Metformin & salicylic acid	Anti-acne	Topical	Acne Vulgaris
MuscleCare™ Pain Relief Therapy vs. Voltaren® in the Relief of Trapezius Trigger Point Musculoskeletal Pain.	Phase 4 (Complete)	MuscleCare Topical Product, Voltaren Topical & Nivea, Topical Cream	Anti-inflammatory	Topical	Myofascial pain syndromes

The clinical study works are carried forward on various drugs, in which the fenugreek wraps with the combination of diclofenac gel was used in the treatment of osteoarthritis of knee, in which the herbal drug study has been completed while the other synthetic drugs used in clinical research has been still under development or terminated. There are several herbal drug emulgels are reported in which few drugs are listed in below Table 5.

Table 5. Reported herbal drug emulgels and their efficacy

Herbal Drug	Category	Route Of Administration	Result	Reference
Aloe vera	Anti-microbial	Topical (Emulgel)	Showed good antimicrobial effect.	[49]
Basil	Anti-microbial	Topical (Emulgel)	Showed the highest wound healing percentage when compared to commercial products.	[50]
Clove-Cinnamon	Anti-fungal & Anti-inflammatory	Oral (Emulgel)	compared to a commercially available marketed medication based on its ability to treat denture stomatitis with an antifungal activity.	[51]
Curcumin	Anti-tumour	Oral (Emulgel)	Emulgel showed pseudoplastic behaviour.	[52]
Ginger	Anti-inflammatory	Topical (Emulgel)	Demonstrated a beneficial interaction between ginger extract and sesame oil.	[53]
Lemongrass	Anti-bacterial	Topical (Emulgel)	Showed good antibacterial effect.	[54]
Lycopene	Anti-ageing	Topical (Emulgel)	Enhanced the skin hydration and elasticity.	[55]

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Paracress	Anti-bacterial	Topical (Emulgel)	Showed maximum antibacterial effect against E. Coli.	[56]
Propolis	Anti-allergic	Topical (Emulgel)	The concentration of emulsifying agent had more pronounced effect on propolis release.	[57]
Resveratrol	Anti-fungal	Intranasal (Nano Emulgel)	Permeation enhanced Bioavailability enhanced.	[58]
Rosemary	Anti-acne	Topical (Emulgel)	Inhibited edema formation after UVB exposure.	[59]

Aloe vera (*Aloe barbidensis*):

The formulation of the aloe vera extract-loaded emulgel utilized to act as penetration enhancers for transdermal effect to cure skin issues. The formulations were subsequently enhanced and examined for antibacterial activity, spreadability factor, thermal analysis, FTIR analysis, in-vivo skin evaluation and in-vitro drug release studies. Optimized emulgel has demonstrated good permeability, prolonged residence time on skin surface and proved good anti-microbial activity and successfully used for treating mild-moderate acne vulgaris and other skin problems. [49].

Basil (*Oscimum basilicum*):

The *Oscimum basilicum*-based emulgel was formulated to evaluate the efficacy of topical application on wound healing. The developed formulations have undergone evaluation for FTIR analysis, accelerated stability studies, physical characteristics determination, rheological behaviour, spreadability factor, patch/ skin sensitivity test and in-vitro drug release studies and comparison with commercially available Silver Sulfadiazine cream Quench®. Therefore, the emulgel exhibited good physical properties and histopathological assessment showed marked improvement in the skin histological architecture [50].

Clove-Cinnamon (*Syzygium aromaticum-Cinnamomum verum*):

A clove and cinnamon oil-loaded emulgel was developed in order to test its effectiveness in treating denture stomatitis by Candida albicans. The evaluation included spreadability test, particle size determination, consistency, in-vitro drug release, in-vivo therapeutic trials, anti-inflammatory, antibacterial, and antifungal activities in the oral cavity. The formulation is compared to commercially available gel, and the optimized formula was successful in reducing denture stomatitis-related inflammation with a better clinical cure rate than commercially available gel, better taste acceptability, and no side effects [51].

Curcumin (*Curcuma longa*):

Incorporating curcumin into the formulation of emulgel could represent a potential strategy for its solubility and distribution of drug into the desired cells for the treatment of oral cancer. The different factors which include mechanical and rheological qualities, in-vitro drug release profile, permeability and cytotoxic potential were assessed. Curcumin's physicochemical characteristics, subsequent release and penetration to specifically kill cancer cells could be enhanced by adding curcumin to emulgel systems [52].

Ginger (*Zingiber officinalis*):

The ginger extract emulgel was formulated to examine by developing niosomal vesicles, a promising nano-carrier, and incorporating them into a sesame oil-prepared formula allows for transdermal distribution. Several formulations were designed in which various investigations were performed such as viscidity, particle size determination, in-vitro release & ex-vivo drug release and the in-vivo anti-inflammatory activity were evaluated. Therefore, this study implies that adding a niosomal formulation to a sesame oil-based emulgel would be a feasible plan for achieving ginger extract's potential for effective transdermal anti-inflammatory activity [53].

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Lemongrass (*Cymbopogon citratus*):

The lemongrass oil and extract were combined to develop a topical emulgel product. The formulation's spreadability, physical properties, stability, pH, in-vitro & in-vivo drug release studies, in addition to it the sun protection factor (SPF) rating were also assessed. According to the study, lemongrass and olive oil may be advantageous in terms of application and stability and is simple to create in pharmaceutical facilities. Additionally, it would be beneficial for daily use due to its overall acceptable qualities [54].

Lycopene:

The lycopene-based topical emulgel was developed by utilizing non-invasive in vivo techniques and sensory evaluation, investigate its effects on the biophysical characteristics of human skin. The emulgel formulation had significantly enhanced the skin hydration and elasticity. Commercial applications of the emulgel formulation included accelerating the aging process, treating oxidative stress-related skin problems and topical infections like acne [55].

Propolis:

The propolis emulgel was formulated to develop for the treatment of burn and wound. Various formulations were prepared and evaluated for physical properties, pH levels, propolis content, viscosity study and in-vitro propolis release. The cumulative amount of propolis release from liquid paraffin and isopropyl palmitate emulgels was investigated. The emulgel formulation was investigated for its wound and burn healing activity in rats. The prepared emulgels showed acceptable physical properties concerning color, homogeneity, consistency, and pH value. Therefore, the formulation is the better management of wounds and burn [56].

Paracress (*Spilanthe acmella*):

For the treatment of bacterial skin diseases, the paracress herbal formulation of the emulgel was developed. Many parameters including physical properties, pH, viscosity, bioadhesive strength estimation, spreading coefficient, antioxidant, extrudability and antibacterial activity, for the emulgel formulation have been assessed. Significantly antibacterial effects were observed in all extract-containing emulgels, the study recommends using paracress-based emulgel to treat bacterial skin infections is beneficial [57].

Resveratrol:

Resveratrol nasal nano-emulgel was developed to investigate the in-vitro release, the drug release kinetics, FTIR, ex-vivo penetration, toxicity and in-vivo pharmacokinetic studies. A well-designed technology to target the brain, the improved nasal nano-emulgel established intranasal safety and bioavailability increase [58].

Rosemary (*Rosmarinus officinalis*):

The rosemary emulgel was developed to stop UVB rays from damaging the skin and to investigate the in vivo effects of an emulgel containing rosemary oleoresin protecting against UVB rays. The results showed that the main components of rosemary oleoresin were rosmarinic acid, carnosic acid & carnosol, and showed that the topical formulation containing rosemary oleoresin prevented the development of edema, myeloperoxidase activity, GSH depletion, and preserved the skin's ability to reduce ferric (Fluorescence Recovery After Photobleaching) and scavenge ABTS (Chemical Compound) after exposure to UVB radiation [59].

CONCLUSION

Emulgel is an innovative drug delivery method which exhibits various beneficial properties such as bypassing the first pass metabolism, better loading capacity, controlled release of the drugs, etc. Due to the advancement of the drug delivery systems in recent years, emulgel have become widely popular in the novel drug delivery technologies. Both the emulgel and nanoemulgel formulations are compared for the better choice, in which both formulations exhibit very few limitations as compared to creams, lotions, etc. The both formulations have been reported in past works with synthetic and herbal extract-based drugs. According to the studies reported on various drugs showed better efficacy and stability. By comparing both the synthetic and herbal emulgels, we observe that the synthetic drugs showed high stability & efficacy and the herbal drugs showed high safety and effect, similarly the synthetic drug was found unsafe to the patient and herbal drug had stability problems. So, we can conclude that the combination of synthetic and herbal extract emulgels can

potentially show higher safety, efficacy and stability. Presently the marketed formulations available for topical use are prepared from the synthetic drugs, which on continuous usage cause various side effects, as to overcome this major drawback, we can use herbal and synthetic drug combination for the scope of future generations regarding safety and stability.

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