

ADVANCES IN EMULGEL AS A TOPICAL DRUG DELIVERY SYSTEM

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ABSTRACT

Emulgels, a type of biphasic semisolid formulation, have surfaced as a promising method for topical drug delivery. They combine the advantages of both emulsions and gels, resulting in a formulation that is both non-greasy and easy to apply, capable of delivering hydrophilic and lipophilic compounds alike. Studies have demonstrated that emulgels can address the challenges associated with conventional gels and emulsions, such as their inability to effectively transport hydrophobic medications and diminished stability during storage. The essential principles governing emulgel systems are based on physicochemical principles, and their features, including thixotropy, non-greasy properties, and emollient qualities, render them an excellent option for dermatological uses. Emulgels have effectively been utilized to transport various medications, such as amlodipine besylate, amphotericin B, and diclofenac sodium. Due to their capacity for controlled release,

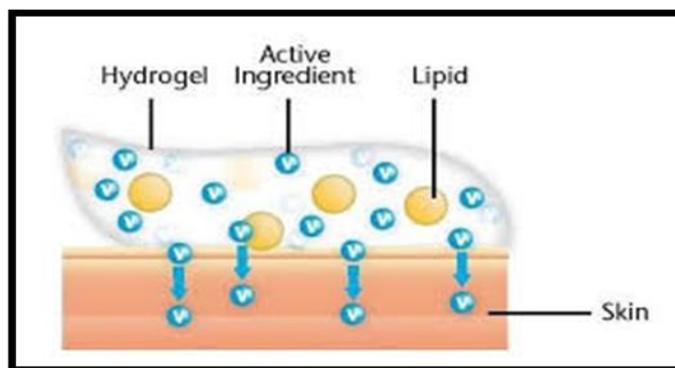
increased stability, and better patient adherence, emulgels have the potential to transform topical drug delivery. More research is necessary to thoroughly investigate their capabilities and tackle existing formulation and characterization challenges.

KEYWORDS: Emulgels, topical drug delivery, controlled release, stability, patient compliance.

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INTRODUCTION

Emulgels are emulsions, categorized as either oil-in-water or water-in-oil types, that become gel-like when mixed with a gelling agent.^[1] Despite the many benefits of gels and emulsions, a significant drawback is their inability to effectively deliver hydrophobic medications and their reduced stability during storage. To address these challenges, Emulgel is utilized to successfully integrate hydrophobic drugs while benefiting from the distinct characteristics of gels.^[2] Since Emulgel has characteristics of both an emulsion and a gel, it functions as a binary controlled release system. Emulgels are a type of biphasic semisolid formulation. They provide the ability to deliver both hydrophilic and lipophilic compounds due to the presence of both water-based and non-water-based phases. Its non-greasy nature makes it ideal for application on the skin compared to other topical formulations like ointments and creams, which can be thick and require excessive rubbing.^[3] It is generally understood that the effectiveness of any topical medication depends on its ability to penetrate the skin. The penetration process into the skin is facilitated if the emulsion is thixotropic, meaning it becomes less viscous when subjected to shear. Consequently, it is integrated into a gel to enhance both emulsion stability and penetration ability.^[4] Additionally, Emulgel intended for dermatological applications possesses numerous beneficial traits, such as being thixotropic, non-greasy, easily applicable, and simple to remove. It is also emollient, does not stain, is water-soluble, has a shorter shelf life, is environmentally friendly, and features a clear and appealing appearance.^[5,6]



"Fig. 1" Emulgel.

FUNDAMENTAL PRINCIPLES OF EMULGEL SYSTEMS

The fundamental operation of emulgel systems is based on the complex interactions among their components, largely governed by physicochemical principles. For example, electron-phonon interactions within these systems can greatly influence their thermal and mechanical characteristics, thereby affecting their performance across diverse applications.^[7] Gaining insight into these interactions is essential for enhancing emulgel formulations.

Furthermore, concepts related to optical flow estimation can shed light on the dynamic behaviors of emulgel systems when subjected to flow conditions. This is especially pertinent in drug delivery applications, where flow behavior may alter the release profiles of active ingredients.^[8,9] The measurement of flow dynamics in relation to emulgel properties continues to be a vital area for future investigation.

ADVANTAGES OF EMULGEL^[10,11,12]

- Transport of hydrophobic medications
- No need for extensive sonication
- Increased loading capacity
- Controlled release
- Affordable preparation expenses
- Enhanced stability

DISADVANTAGES OF EMULGEL^[13]

- Difficult to penetrate the skin due to large particle size
- Limited permeability for certain medications
- Potential skin irritation or allergic reactions from contact dermatitis
- Formation of bubbles during emulgel creation

FORMULATION STRATEGIES OF EMULGELS

Selection of Oil Phase, Surfactants, Emulsifiers and Gelling agents.

Oil Phase Selection

The selection of the oil phase is crucial in emulgel formulations, affecting the solubility and release properties of drugs. Studies have shown that various oil phases, including castor oil and octanoic acid, significantly influence the stability and sensory qualities of the formulations.^{[14], [15]} For example, it is emphasized that solubility studies are essential in

choosing an appropriate oil phase, which is vital for improving drug solubility and bioavailability.^[15]

Beyond traditional oils, innovative alternatives like squalene have been investigated within emulsion systems. A squalene-based emulsion adjuvant has been proposed, showcasing the promise of novel oil phases to enhance formulation stability and efficacy.^[16] Future investigations could aim to assess a broader range of oil phases, both natural and synthetic, to determine their compatibility with specific therapeutic uses.

“Tab. 1:” Examples of oils used in Emulgel formulation.

Name of oils	Properties	Reference No.
Balsam oil	Antifungals, topical antibiotics	[17]
Birch oil	Topical NSAIDs, corticosteroids, anti-microbials	[18]
Castor oil	Topical NSAIDS, antioxidants	[19]
Geranium oil	insecticidal and anti-bacterial	[20,21]
Isopropyl myristate	Drugs for acne, topical steroids	[22,23,24]
Myrrh oil	Antifungal, antiviral	[25]
Olive oil	Antioxidant, antimicrobial	[26,27,28]
Rose hip oil	Topical steroids, topical NSAIDs, drugs	[29,30]
Thyme oil	Topical antibiotics, topical NSAIDs	[31,32,33,34]
Wheat germ oil	Topical steroids, topical NSAIDs, drugs for psoriasis	[35,36,37]
Wool wax	Antimicrobials, antifungal	[38]

Surfactants and Their Role

Surfactants are essential for stabilizing emulgels as they lower interfacial tension and improve emulsification. The choice of surfactants should be specifically tailored to the oil phase and active ingredients to ensure optimal effectiveness. For instance, combining Tween 20 with castor oil has been demonstrated to improve the emulsification process. Additionally, the ratio of surfactant to cosurfactant greatly affects the properties of nanoemulsions, which are closely associated with emulgels.^[14]

Emulsifiers and their purpose

Emulsifying agents are utilized to facilitate emulsification during manufacturing and to ensure stability throughout the product's shelf life. The choice of emulsifying agents is based on the formulation and its HLB value. Emulgel formulations are created using Tween as the emulsifying agent in the aqueous phase and Span 20 in the oily phase. Examples include Polyethylene glycol 40 stearate, Sorbitan monooleate (Span 40), Polyoxyethylene sorbitan monooleate (Tween 80), Stearic acid, and Sodium stearate.^[39,40]

Gelling Agents in Emulgels

The use of gelling agents is crucial for obtaining the desired viscosity and stability in emulgels. Selecting the appropriate gelling agents can influence the release characteristics of the active ingredients, thus affecting their therapeutic effectiveness. Research shows that the interaction between surfactants and gelling agents plays a vital role in creating stable emulgels.^[41]

Nevertheless, there is a significant lack of comprehensive studies examining various gelling agents alongside different oil phases and surfactants. Future research should concentrate on investigating the rheological characteristics of emulgels made with different gelling agents to gain deeper insights into their effects on drug release and stability.

“Tab. 2:” Examples of Gelling agents used in Emulgel formulation.

Gelling agents	Advantages	Concentration	Ref. No.
Carbopol 934	Form gels at very low concentrations & provide controlled release of incorporated drug	1%	[42,43]
Carbopol 940	Form highly viscous gels and provide controlled release of incorporated drug	1%	[44,45]
HPMC	Produce neutral gels of very stable viscosity, microbial resistance & good film strength	2.5%	[46,47]
HPMC + Carbopol	Combination produces more stable emulsion in comparison with individual gelling agents	1.2%	[48,49]
Pluronic® F127	Have better solubility in cold water with good clarity	1–3%	[50]
Pemulen	Has excellent stability, low irritancy and provides rapid release of oil phase	0.1–0.4%	[51]

PREPARATION OF EMULGEL

The methodology for preparation of emulgel includes three ways.

Step 1: Formulation of the gel base

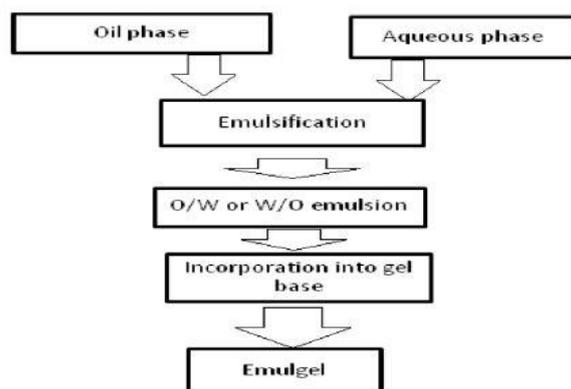
The gel phase is created by dissolving the polymer in purified water while continuously mixing at a moderate speed using a mechanical shaker. The pH is adjusted to a range of 6 to 6.5 using triethanolamine or NaOH.

Step 2: Preparation of o/w or w/o type emulsion

The oil phase of the emulsion is prepared by dissolving an emulsifier, such as Span, in an oil medium like liquid paraffin, while the water phase is created by dissolving a hydrophilic emulsifier, such as Tween, in purified water. Methyl paraben and propyl paraben are

dissolved in a humectant like propylene glycol, while the drug is dissolved in ethanol, and both prepared solutions are combined with the aqueous phase with careful mixing. The oily and anhydrous phases are gently heated to between 70°C and 80°C; the oily phase is then added to the anhydrous phase while maintaining constant mixing. This mixture is allowed to cool down to room temperature.

Step 3: In the subsequent step, the emulsion is integrated into the gel base with continuous stirring, mixing the gel phase into the emulsion phase in a 1:1 ratio to create an emulgel.^[52,53]



"Fig. 2:" Formulation steps of Emulgel.

CHARACTERIZATION OF EMULGELS

Physicochemical Characterizations

Viscosity and Rheological Properties

Viscosity is a fundamental physicochemical characteristic of emulgels that significantly impacts their use in drug delivery. Utilizing high-intensity ultrasound can improve the emulsifying characteristics of protein-based systems, resulting in enhanced rheological properties and greater stability of emulsions.^[54] This is especially important for emulgels, where viscosity influences the drug release profile and its ability to permeate biological membranes. Additionally, the relationship between viscosity and flow behavior affects the application's ease and ultimately, patient compliance.^[55]

Stability and Formulation

The stability of emulgels is a crucial physicochemical characteristic that affects their longevity and effectiveness. Research has indicated that the selection of formulation ingredients, including surfactants and stabilizers, plays a significant role in determining the stability of emulgels.^[56] For example, incorporating certain nanoparticles has been found to

improve the stability of drug formulations by reducing sedimentation and aggregation.^[57] Nonetheless, the long-term stability and degradation processes of emulgels have not been thoroughly studied, revealing an important gap in the existing literature.

Elasticity and Mechanical Properties

The mechanical characteristics, such as elasticity, of emulgels play a crucial role in their use, especially in wound healing applications. This underscores the significance of mechanical properties in drug delivery systems aimed at wound healing, indicating that a balance between flexibility and strength is crucial for achieving optimal results.^[58] The elasticity of an emulgel can influence its adherence to the skin and its capacity to adapt to various wound shapes, consequently affecting the kinetics of drug release and the effectiveness of treatment outcomes.

Interaction with Biological Systems

Understanding the interaction of emulgels with biological systems is crucial for evaluating their effectiveness. Research has indicated that factors such as the size and surface charge of nanoparticles can greatly influence their interactions with biological entities.^[59] This interaction may modify the drug release profiles from emulgels and their later absorption by biological tissues. The consequences of these interactions for the design and formulation strategies of emulgels require more in-depth exploration.

“Tab. 3:” Current investigations in emulgel using different drugs.

Drug	Use	References
Amlodipine besylate	Transdermal delivery	[60]
Amphotericin B	Leishmaniasis therapy	[61]
Betamethasone dipropionate	For the treatment of atopic dermatitis	[62]
Calcipotriol	In the treatment of psoriasis.	[63]
Cyclosporin A	Topical ocular delivery	[64]
Diclofenac sodium	Management of pain	[65]
Diclofenac sodium	Pain relief	[66]
Ketoprofen	Anti-inflammatory	[67]
Lacidipine	Antihypertensive	[68]
Metronidazole and ciprofloxacin	Passive and iontophoretic delivery of therapeutics	[69]
Meloxicam	Anti-inflammatory	[70]
Nimorazole	Hypoxic cell radiosensitizing agent	[71]
Terbinafine hydrochloride	In the treatment of fungal infection	[72]

“Tab. 4:” Marketed formulations of emulgels.

Drug	Marketed product	Manufacturer
Azithromycin	Avindo gel	CosmePharma Lab.
Aceclofenac, Methyl salicylate, Capsaicin	Acent gel	Intra Labs India Pvt. Ltd.
Benzoyl peroxide	Pernox gel	Cosme Remedies Ltd.
Clindamycin, Adapalene	Excec gel	Zee Laboratories
Diclofenac diethyl ammonium	Voltaren emulgel	Novartis Pharma
Miconazole nitrate, Hydrocortisone	Miconaz-H-emulgel	Medical Union Pharmaceuticals

THERAPEUTIC APPLICATIONS

Enhanced Drug Delivery

Emulgel formulations have been recognized for their ability to improve the delivery of bioactive compounds. For example, nanocurcumin—a formulation derived from curcumin—shows considerable therapeutic advantages thanks to its improved solubility and bioavailability.^[73] This is consistent with research that explores how permeation enhancers in transdermal drug delivery can enhance drug absorption through the skin, indicating that emulgel formulations are especially appropriate for topical applications.^[74]

Wound Healing and Skin Regeneration

Innovative delivery systems for growth factors play a vital role in wound care and skin restoration. Emulgel formulations can enable the gradual release of growth factors, thus aiding the healing process.^[75] This use is particularly important in medical environments where swift tissue regeneration is necessary. Additionally, multifunctional nanoparticles improve imaging and medication delivery in therapeutic applications, indicating that emulgel formulations might function as vehicles for these sophisticated delivery systems.^[76]

Antioxidant and Anti-inflammatory Properties

The healing properties of natural substances included in emulgel preparations have been investigated as well. Quercetin, known for its considerable antioxidant and anti-inflammatory properties, offers various health benefits. By incorporating such compounds into emulgels, their therapeutic effectiveness could be improved, serving both as a method for drug delivery and as a source of pharmacological activity.^[77]

Cancer Therapeutics

The promise of emulgel formulations in cancer treatment is significant. Nanoparticles that target tumors for concurrent diagnosis and therapeutic evaluation imply that comparable strategies might be tailored for emulgel formulations to enhance targeted drug delivery in

cancer-related applications.^[78] This is in line with the increasing emphasis on personalized medicine and the necessity for precision in cancer treatment methods.

Nutraceutical Applications

The incorporation of bioactive substances such as resveratrol into emulgel formulations can be further investigated for their health benefits. Clinical evidence was identified that supports the use of resveratrol, which might be effectively administered through emulgel systems, thereby increasing its therapeutic potential.^[79]

FUTURE PERSPECTIVE

Transdermal Drug Delivery: Emulgels may be designed to promote transdermal drug delivery, enabling controlled and sustained release of medications through the skin, which could potentially substitute traditional oral or injectable methods for certain treatments.

Individualized Skincare: With the progress in skin analysis and diagnostics, emulgels could be customized for specific skin types and conditions. These personalized formulations might yield improved skincare outcomes.

Research in advanced Drug Delivery is expected to focus on creating emulgels capable of effectively delivering a broader spectrum of medications, including those with low solubility, to designated sites within the body. This could result in more effective therapies for various medical conditions.

Nanotechnology Integration: The combination of nanotechnology with emulgels could allow for the encapsulation of nanoparticles carrying drugs or other bioactive substances. This could improve targeted delivery and the controlled release of therapeutic agents.

Incorporation of Active Ingredients: Emulgels have the potential to include innovative active components, such as peptides, growth factors, and stem cell extracts, to target particular skin issues and enhance skin wellness.

Sustainability and Natural Ingredients: The movement towards eco-friendly and natural products may influence the creation of emulgels that utilize sustainable ingredients and maintain a minimal environmental footprint.

CONCLUSION

In conclusion, the progress made in emulgel technology marks a considerable advancement in the creation of efficient topical drug delivery systems. By overcoming the shortcomings of conventional formulations and utilizing cutting-edge technologies, nano-emulgels offer significant potential for enhancing therapeutic results. Nonetheless, additional research is crucial to tackle current challenges, investigate new applications, and refine formulations for clinical implementation. Future research efforts should focus on assessing stability, evaluating pharmacokinetics, and incorporating emerging technologies to fully harness the capabilities of emulgels in the field of medicine.

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