Journal of Pharmaceutical Research International

33(62B): 258-268, 2021; Article no.JPRI.80026
ISSN: 2456-9119
(Past name: British Journal of Pharmaceutical Research, Past ISSN: 2231-2919, NLM ID: 101631759)

Overview of Emulgel as Emergent Topical Delivery: Recent Applications and Advancement

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JPRI/2021/v33i62B35565

Open Peer Review History:
This journal follows the Advanced Open Peer Review policy. Identity of the Reviewers, Editor(s) and additional Reviewers, peer review comments, different versions of the manuscript, comments of the editors, etc are available here: https://www.sdiarticle5.com/review-history/80026

Review Article

Received 24 October 2021
Accepted 28 December 2021
Published 29 December 2021

ABSTRACT

Emulgel is an emerging delivery system with added advantages over other topical delivery systems which is proven to be boon for cosmetics and dermatology. Emulgels are emulsion which is converted to Gel, which will make it a non greasy and enhances patient compliance. The amalgamation of the two systems would be advantages in term of high drug loading capacity and low skin irritation, site specific targeting avoiding first-pass metabolism and increase in bioavailability. Work carried out by researchers proved that, Emulgel/ Nanoemulgel loaded with drugs has been found effective in many topical disorders and it is emerging as potential drug delivery system in area of dermatology. In the present review current research works that carried out on Emulgel and nano emulgels are discussed and also highlighted the recent applications of Emulgel in transdermal as well as dental, ocular, vaginal, and other delivery system.

Keywords: Emulgel; nano emulgel; topical delivery system; emulsion; dermatology.

1. INTRODUCTION

Recent years witnessed the popularity of transdermal drug delivery systems such as ointments, creams, gels, lotions because they lacks drawbacks associated with oral, parenterals, nasal and other modes of drug delivery [1], Many disadvantages associated with

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these traditional types of topical preparations such as stickiness, pourability, lack of spreadibility, stability issue leading to patient incompliance. 1980-90 was the era of popularity of Emulsion and Gel in pharmaceutical topical semisolid dosage form due to its wide applications in dermatology. Emulsions are commonly used for topical pharmaceutical and cosmetic products, such as lotions and creams. Emulsions can be designed to facilitate drug penetration into and/or through the skin. Both oil-in-water and water-in-oil emulsions have been extensively used to deliver drugs and cosmetic agents to the skin, depending on the property of active agents and the indications of the medicines. Emulsions possess certain degree of elegance and get easily washed off. Emulsions have a high ability to penetrate the skin. Regardless of lots of advantages of emulsion, topical application is limited due to its low viscosity and spreadibility.

Gels for topical use have several favorable properties such as greaseless, thixotropic, easily spreadable, easily removable, emollient, non-staining, compatible with many additives, and water-soluble or miscible In spite, so advantageous gels show a major limitation in the delivery of hydrophobic drugs [2]. The majority of the newer drugs developed are lipophilic in nature resulting in unpredictable absorption, poor oral bioavailability, and also variation in pharmacokinetics. Emulgel, an emerging topical delivery system has proved to boon for the delivery of lipophilic drugs over other formulations.

With the advancement and modernization in transdermal delivery over the years emulgels are gaining interest both in pharmaceutical and cosmetics industry due to greater patient compliance and improved efficacy.

Emulgels are matrices of polymeric gels into which oil phase is incorporated which increases its stability and makes it a dual control release system for hydrophilic and hydrophobic drugs [3], Nanoemulgels are oil-in-water nano emulsions gelled with the use of some gelling agent in it and possess the advantages of both emulsions and gels. Nano emulgels has many advantages such as, transparent, good appearance, greaseless, better spreadability, easily washable, thixotropic, emollient, nonstaining, longer shelf life and. [4], another merits are site specific targeting avoiding first-pass metabolism and ultimately increasing bioavailability as shown in Fig. 1.

The amalgamation of the two systems makes emulgel formulation advantageous in many ways such as, high drug-loading capacity, low skin irritation, easy incorporation of lipophilic drugs and increase in skin permeability and ultimately, the pharmacokinetic and pharmacodynamic profiles of the lipophilic drugs are improved significantly [5].

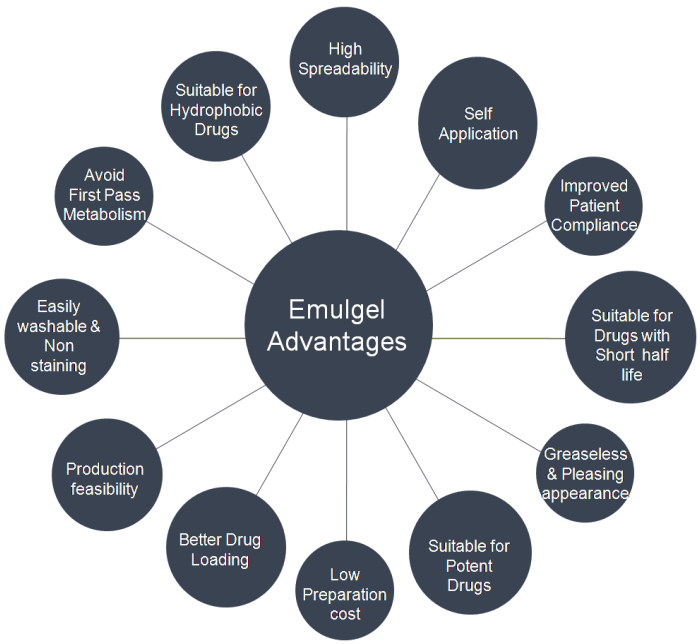

Fig. 1. Advantages of emulgel delivery system

The nanoemulsion component of the nanoemulgel helps in protection of drug by preventing the enzymatic degradation. The gel base by increasing the viscosity of the aqueous phase by decreasing the interfacial and surface tension provides thermodynamic stability. Nanoemulgels possess rheological characteristics which are important for transdermal as well as topical delivery such as buccal, dental etc. with the aid of better patient acceptance [6].

In the present scenario, emulgel and nanoemulgel formulation can be considered as potential and promising candidates for topical delivery of lipophilic drugs in the future.

This review aims to introduce the latest trends and applications in transdermal drug delivery via Emulgel for topical and transdermal drug delivery.

2. TOPICAL APPLICATIONS

Nanoemulgel preparations of many drugs are being used successfully in different areas of health care such as food supplement, cosmetics, pharmaceuticals and proved its significance in topical and other route of delivery.

Sungpud C, et al. [7], evaluated and compared techno-biofunctional characteristics of nanoemulsion and nanoemulgel loaded with mangostin extracts. They concluded that, nanoemulgels had a higher mangostin release than emulgels and presented the feasibility of nanoemulsions and nanoemulgels loaded with mangostin extracts as a promising delivery system for bioactive polyphenol in food supplements, pharmaceuticals and cosmetics. Nanoemulgel preparations of many approved drugs are used in different areas of health care and point out the significance of topical route of delivery as compared to other routes. Torregrosa A, et al. [8], developed an metronidazole emulgel for the treatment of rosacea (blushing or flushing and visible blood vessels), applying quality by design (QbD) and found that the emulgel releases metronidazole faster than the creams as it provides greater time of residence over the affected facial area. Anand K, et al. [9], reviewed extensively on nanoemulgel and found to be a promising system compared with nanolipoidal formulations. They stated that, Nanoemulgel can be applicable to various acute and chronic diseases through topical routes. Jagdale SC et al. [10], formulated emulgel with controlled delivery of mupirocin using Sepineo P 600 for the treatment of skin infection. Antimicrobial and anti-inflammatory study proved successful development of stably controlled release mupirocin emulgel. The optimized batch showed comparable results with marketed formulation against *Staphylococcus aureus.*

Ali Khan B, et al. [11], formulated and evaluated the efficacy of topical application of OB-based emulgel on wound healing in animal model. The wound healing effect was evaluated and compared with commercially available Silver Sulfadiazine cream Quench® in wound-induced rabbits by macroscopic and histopathological evidence. Histopathological assessment showed marked improvement in the skin histological architecture after 16 days of OB emulgel treatment. Nordholm-Carstensen A et al. [12], compare the standard treatment, diltiazem gel 2%, with Levorag® Emulgel for chronic anal fissures in a single-blinded, randomised, controlled, clinical trial with a non-inferiority design. Patients with a chronic anal fissure were randomised to treatment with diltiazem or Levorag® Emulgel twice daily for 8 weeks. The study demonstrated statistical non-inferiority of Levorag® Emulgel compared with diltiazem in the treatment of chronic anal fissure. Balata GF et al. [13], developed an alternative medicine, propolis, in emulgel formulation for burn and wound treatment. The optimized formulation found to be a promising formula for better management of wound and burn.

Mohamed MI, et al. [14], formulated zolmitriptan (Zol) niosomal vesicles to potentiate its transdermal effect. The optimized formulation was formulated in Emulgel (1:1 emulsion/gel ratio). Niosomal loaded emulgel showed thixotropic behavior of significant bioavailability and pharmacokinetic parameters as compared to the plain Zt-loaded Emulgel. Surini S, et al. [15], prepared Recombinant human epidermal growth factor (rhEGF) loaded transfersomal emulgel with enhanced skin penetration compared with that of non-transfersomal rhEGF emulgels. The skin penetration of rhEGF was enhanced by as much as 5.56 fold by transfersomal emulgel compared with that of non-transfersomal Emulgel.

Shanmugarajan TS, et al. [16], developed a squalene loaded emulgel-based system as a approach for potential skin regeneration. They concluded that the squalene-loaded emulgel scaffold could be an effective formulation used in the treatment of the burnt skin tissue defects.

The squalene-loaded emulgel scaffold showed outstanding contraction of wound as compared with the agar gel and negative control. Burki IK, et al. [17], designed and developed dexibuprofen-capsaicin emulgel (DC emulgels) for transdermal drug delivery with improved anti-inflammatory and analgesic effects. The DC emulgel showed good physical appearance and stability. The research study also concluded that synergistic potential of DC emulgel could be an alternative to the conventional topical dosage form. Ahmad J, et al. [18], designed a thymol loaded nanoemulgel preparation by exploiting low-energy emulsification method for topical application in acne. The study found that the prepared emulgels has improved moisturising properties.

Arshad W, et al. [19], developed phyto-cosmetic emulgel of C. tamala leaves extract and reported that, as compared to placebo, prepared emulgel was found to be effective in minimizing skin photo-damaging effects. Malavi S, Kumbhar et al. [20], developed tretinoin (TRT)-loaded topical emulgel formulation using 32 optimal response surface design (ORSD) the optimized TE displayed significant *in vivo* anti-inflammatory activity when compared to marketed gel. Pal RR, et al. [21], prepared and evaluated levocetirizine loaded emulgel containing tamanu oil and sericin for atopic dermatitis. *In vivo* pharmacodynamic studies revealed enhanced therapeutic potential of emulgel when compared with conventional gel. Khiljee T, et al. [22], formulated a stable *Pyrus communis* fruit extract emulgel which, showed excellent antioxidant and anti-tyrosinase activities. From findings it is concluded that *Pyrus communis* fruit extract loaded emulgel possesses antiaging potential with improvement in skin tone and elasticity. Pinheiro IM et al. [23], has develop an emulgel of Amphotericin B and showed potential activity against the *in vitro* parasite with significant reduction of cytotoxicity on murine macrophages, indicating that emulgels formulation is promising for the treatment of cutaneous leishmaniasis.

Coêlho ES, et al. [24], developed and characterized a topical emulgel of amphotericin with bacuri butter (*Platonia insignis Mart*.) and evaluate its antileishmanial activity wich showed reduction on cytotoxicity to host cells. Sparavigna A, et al. [25], evaluated the vasokinetic activity of a Visnadine Emulgel on mucosal genitalia of 15 healthy postmenopausal women clinically. Visnadine Emulgel single application showed significant increase of vulvar hyperemia, along with a significant increase of local turgor versus placebo. Gusai T, et al. [26], prepared acyclovir-loaded microsponge-based emulgel to improve its topical delivery. The results of the *ex vivo* permeation study proved significant improvement in drug permeation from optimized microsponge-loaded emulgel compared to the marketed formulation. Mohammadi S, et al.[27], compared physicochemical stability and clinical anti-wrinkle efficacy of transdermal emulgel preparations of sodium ascorbyl phosphate (SAP) and ascorbic acid (AA) on human volunteers. Formulations containing (AA) and or (SAP) both improved elasticity and wrinkles of the skin. Tasneem R, et al. [28], formulated a stable and effective *Albizia lebbeck* bark extract loaded o/w emulsion based emulgel for antioxidant activity and concluded significant antioxidant effects on human skin of prepared emulgels.

Sainy J, et al. [29], has developed an Aloe vera-based emulgel formulation of Desoximetasone (DM) for effective treatment of plaque psoriasis and found to increase in *in vitro* permeation of drug from Aloe vera emulgel and could be employed for the topical treatment of skin ailments. de Lafuente Y, et al. [30], evaluated the influence of the incorporation of caffeine in bioadhesive emulgel formulationand results suggested that the optimized emulgel could be an interesting topical biodhesive delivery system for cosmetic applications. Morsy MA, et al. [31], formulated and evaluated the efficacy of topical application of ATR-based nanoemulgel on wound healing. Sithole MN, et al. [32], have developed nano-emulsions and nano-emulgels of statins via the transdermal route. The results indicated the benefits of nano-emulsions and nano-emulgels as potential alternative delivery systems for the transdermal delivery of statins. El-Salamouni NS, et al. [33], evaluated the efficacy of chamomile oil and nanoemulgel formulations for atopic dermatitis. Treatment with nanoemulgels showed significant decrease in duration of skin healing and no spongiosis compared to chamomile oil. Ijaz S, et al. [34], designed the polyphenolic contents of *Mimosa pudica* (MP) seed extract stable topical emulgel formulation and concluded that, the topical emulgel preparation loaded with MP seed extract could be a best option to deal with dematoheliosis.

Meer S, et al. [35], investigated the skin depigmenting and antierythmetic effects of *Annona muricata L.* fruit extract emulgels and results revealed increase in the skin whitening effects. Hamed R, et al. [36], has developed

nanoemulsion-based gel (NE gel) formulation of diclofenac diethylamine (DDEA) for topical administration. The release of DDEA from conventional gel, emulgel and NE gel showed a controlled release pattern over 12 h, which was consistent with the rheological properties of the gel. Khan Q, et al. [37], Developed dimenhydrinate (DM) emulgel formulation with enhanced permeation for transdermal delivery of DM in treatment of motion sickness. Abdallah MH, et al. [38], evaluated a nanoemulgel formulation of Brucine for enhanced topical anti-inflammatory and anti-nociceptive activities. Results suggested that myrrh oil-based nanoemulgel might represent a promising delivery vehicle for potentiating the anti-inflammatory and anti-nociceptive actions of brucine. Mwangi AN, et al. [39], formulated and evaluated meloxicam emulgels as a potential alternative topical treatment option for rheumatism. Soliman WE, et al. [40], has developed Curcumin (Cur) nanoemulgel for transdermal delivery. The *in vivo* anti-inflammatory activity was estimated using the carrageenan-induced rat hind paw edema method and the results concluded that myrrh oil and Cur-loaded nanoemulgel showed the lowest percent of swelling.and thus confirmed the potential of the nanoemulgel dosage form.. Sharma G et al. [41], prepared emulgel of probiotic, Bacillus for topical use. They found faster wound closure and reduction in oxidative stress in comparison to Soframycin®.

Siddiqui B, Rehman AU et al.[42], utilises the proficient function of diacerein (DCR) and anti-inflammatory polymers to develop sustained release nanoencapsulated emulgel for potential use in osteoarthritis (OA). Chitosan (CHS) and chondroitin sulphate (CS) were employed as natural anti-inflammatory polymers to encapsulate nanoformulation of DCR. nanoemulgel sustained release of drug having superior penetration properties with provision of enhanced therapeutic effect owing to the presence of CHS, CS, and Argan oil possessing indelible anti-inflammatory attributes. Tuncay Tanrıverdi S, et al. [43], developed Melatonin-loaded hyaluronic acid (HA) and polyvinyl alcohol (PVA) Freeze-thaw hydrogels and emulgels . *In vitro* release studies showed that the release was improved by emulgel formulations. and concluded that, emulgel formulations could be promising systems for topical application of melatonin. Hariyadi DM, et al. [44], investigated and prepared emulgel mask of *C. nucifera L.* Extract (1%) from Kopyor coconut containing carbomer 940 in various concentration (1% and 1.5%). They reported that, formulation had good spreadability, and also produced highest antibacterial activity against *P. acnes.*

3. OTHER ROUTES

Javed H, et al. [45], formulated diphenhydramine nasal nano-emulgels with better penetration for targeted controlled delivery to mucous membrane. The optimized formulation found to have excellent permeability and prolonged residence time on mucosal surface. Salem HF et al. [46], formulated nasal nano-emulgel of resveratrol, employing Tween 20, Capryol 90, and Transcutol in emulsion phase and carbopol 934 and poloxamer 407 as the gelling agents. They stated that nano-emulgel has the advantages of both gels and nano along with the intranasal safety and increase in the bioavailability and could be considered as delivery system to target the brain.

Sabry HS, et al. [47], formulated an ophthalmic emulgel of combination of betamethasone sodium phosphate and levofloxacin. The new combination in emulgels showed extended release of the two drugs which potentially improve resident time in ocular tissues, patient compliance, and adherence to treatment. Rawooth M, et al. [48], developed tamarind gum (TG) and rice bran oil (RBO)-based emulgels of ciprofloxacin HCl and suggested a significantly lower release from the emulgel matrices. The emulgels were able to improve the corneal permeation of drug and thus could be explored to deliver drugs to the internal structures of the eye.

Badawi NM, et al. [49], clinically compared the efficiency of metronidazole (MTD) loaded solid lipid nanoparticles (SLNs) vaginal emulgel with the marketed vaginal gel (Metron®) against Bacterial vaginosis (BV). Clinical studies recorded significant enhancement in therapeutic response of MTD from optimized SLNs vaginal emulgel formulation regarding the clinical treatment and low recurrence rate against the marketed product. De Oliveira Neto AS et al.[50], formulated atorvastatin loaded oral and vaginal emulgels and evaluated the antifungal activity of atorvastatin and concluded that atorvastatin emulgels could be utilized in treatment offungal infection. Golshah A, et al. [51], investigated the gingivitis effectiveness of Resveratrol emulgel in orthodontic patients and found that the prepared Emulgel was effective in improving gingival health in orthodontic patients and in lowering

Table 1. Applications of Emulgel with use and Route of application

Drug	Route	Application	Reference
Mangostin Extracts	Topical Emulgel	Food Supplements, Pharmaceuticals and Cosmetics.	[7]
Metronidazole	Topical Emulgel	Rosacea	[8]
Propolis	Topical Emulgel	Burn and Wound	[13]
Dexibuprofen-Capsaicin	Topical Emulgel	Acne	[17]
C. tamala Leaves Extract	Topical Emulgel	Skin Photo-Damaging Effects	[19]
Tretinoin	Topical Emulgel	Anti-Inflammatory Activity	[20]
Tamanu Oil And Sericin	Topical Emulgel	Atopic Dermatitis	[21]
Pyrus communis Fruit Extract	Topical Emulgel	Antioxidant and Anti-Tyrosinase Activities	[22]
Amphotericin B	Topical Emulgel	Cutaneous Leishmaniasis.	[23]
Amphotericin With Bacuri Butter	Topical Emulgel	Antileishmanial Activity	[24]
Visnadine	Topical Emulgel	Postmenopausal Superficial Dyspareunia:	[25]
Acyclovir	Topical Emulgel	Cold Sores	[26]
Odium Ascorbyl Phosphate & Ascorbic Acid	Topical Emulgel	Antioxidant Activity	[27]
Desoximetasone	Topical Emulgel	Plaque Psoriasis	[29]
Caffeine	Topical Emulgel	Cosmetic Applications	[30]
Atorvastatin	Topical Emulgel	Wound Healing.	[31]
Chamomile Oil	Topical Emulgel	Atopic Dermatitis	[33]
Mimosa pudica (Mp) Seed Extract	Topical Emulgel	Dematoheliosis	[34]
Annona muricata L. Fruit Extract	Topical Emulgel	Cosmetic	[35]
Diclofenac Diethylamine	Topical Emulgel	Analgesic	[36]
Brucine	Topical Emulgel	Anti-Inflammatory and Anti-Nociceptive Activities	[38]
Meloxicam	Topical Emulgel	Rheumatism	[39]
Curcumin	Topical Emulgel	Anti-Inflammatory Activity	[40]
Probiotic*, (Bacillus)*	Topical Emulgel	Faster Wound Closure and Reduction in Oxidative Stress	[41]
Diacerein	Topical Emulgel	Osteoarthritis	[42]
Melatonin	Topical Emulgel	An Anti-Aging and Skin Protective Agent.	[43]
C. Nucifera L. Extract	Topical Emulgel	Antibacterial Activity Against *P. Acnes*.	[44]
Diphenhydramine	intranasal	Nasal Congestion Due to Allergies.	[45]
Resveratrol	intranasal	Brain Targeted Delivery	[46]
Betamethasone Sodium Phosphate and Levofloxacin	Ophthalmic	Ocular Drug Delivery	[47]
Ciprofloxacin Hcl	Ophthalmic	Corneal Permeation	[48]
Metronidazole	vaginal emulgel	Enhancement in Therapeutic Response	[49]
Atorvastatin	vaginal emulgel	Antifungal Activity	[50]
Resveratrol	Oral	Gingival Inflammation	[51]
Curcumin Emulgel	Oral	Oral Cancer	[52]
Itraconazole And Clotrimazole Emulgels	Topical	Sporothrix Brasiliensis	[53]
Furbiprofen	Topical	Arthritis	[54]
Ofloxacin	Topical Emulgel	Site Specific Delivery	[55]

gingival inflammation. Ferreira SBS, et al. [52], prepared curcumin emulgel for the treatment of oral cancer. They developed curcumin emulgels with poloxamer 407, acrylic acid derivatives along with sesame oil or isopropyl myristate as oil phase. They concluded that, the

physicochemical properties, subsequent release and permeation of curcumin to selectivity kill cancer cells could be improved by the incorporation into emulgel systems. Noronha LL, et al. [53], developed itraconazole and clotrimazole emulgels to improve therapeutic effectiveness against Sporothrix brasiliensis. They reported that the prepared emulgel found to be good *in vitro* inhibitory activity against S. brasiliensis yeasts and suggested that the emulgel containing itraconazole and clotrimazole might highly be efficient therapy to oral administration in the treatment of sporotrichosis. Bera H et al. [54], developed FLU-loaded emulgel reliable drug carriers for furbiprofen intrgastric delivery with a view to improve biopharmaceutical characteristics of drug and modulate its release in a controlled manner. All the formulations demonstrated excellent drug encapsulation efficiency and sustained drug release behavior along with the better *in vitro* gastro retention capabilities. Recent applications of emulgel with use and route of application are summarized in Table 1.

4. CONCLUSIONS

Emulgels are greaseless, easy spreadable, removable, thyrotrophic, good appearance, and transparent. In current scenario the emulgels are being used for the delivery of many drugs like analgesics, anti-inflammatory, anti-acne and anti-fungal. Hence, it is of great pharmacological importance and is relatively free of side effects. In the coming years, it will be most commonly used because it is easy to use and enhances patient compliance. After a thorough literature survey, we can conclude that emulgels has proven to be one of the most effective, better and convenient drug delivery systems as emulgels has the ability to deliver hydrophobic as well as hydrophilic drugs. Therefore, this novel transdermal dosage form is open for research to target specific dermatological disorders as well as in the improvement of various systemic ailments.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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Peer-review history:
The peer review history for this paper can be accessed here:
https://www.sdiarticle5.com/review-history/80026