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A Review on Application of Emulgel in Dermatological Diseases

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ABSTRACT
The term "gel" is usually associated with hydrated polymeric network.Two components are present in gel in different proportions, i.e., the solvent and the polymeric solute. The latter are either natural or synthetic polymer able to retain a large amount of the former component. A network of colloidal solid particles holds a vast quantity of aqueous or hydroalcoholic fluid. The major drawback for the gel is that one cannot incorporate poorly soluble drugs in the gel. The rationale for emulgel is to incorporate the lipophilic drug in the oil phase of the emulsion and then convert the emulsion into a gel by adding gelling agent into an emulsion. In this way, the lipophilic drug can be incorporated into the gel. It will increase the application of the gel. Emulgel has properties of emulsion such as sustaining drug action and the gel; increasing retention time. This review focused on the different topical applications of emulgel.
Keyword: Emulgel, Dermatoligiacal disease, inflammation, antibacterial

I. INTRODUCTION

A topical drug is applied on the surface of the human body, such as the skin or the mucous membrane, via a vast extent of dosage form, including creams, foams, gels, lotions, and ointments.Gels containsignificant amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles and generally show better drug release than ointments and creams. However, there is a problem in incorporating hydrophobic drugs in the gel. Emulgel preparations overcome such types of problems, and thereby hydrophobic drugscan enjoy the unique properties of gels. The incorporation of a gelling agent in the water phase transforms a classical emulsion into an emulgel.Both oil-in-water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin.

In an emulsion, the internal phaseacts as a drug reservoir.The drug partition through the external phase and gets absorbed in the skin. Emulgel is a better choicefor BCS class II drugs that show poor solubility and high permeability. Emulgel possesses the properties as thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, water-soluble, long shelf life, biofriendly and satisfying appearance that works on the patient adequacy.

Since the mid-1980s, emulsion gels have been coming under pharmaceutical topical semisolid dosage form. The best thing about emulgel is that both hydrophobic or hydrophilic drugs can be integrated and release the drug in a controlled manner, givingan excellent therapeutic effect as topical drug delivery.

Advantages
1. Incorporation of hydrophobic drugs
2. Improved loading capacity
3. Improved stability
4. Production feasibility and low preparation cost
5. Controlled release of drug
6. No rigorous sonication

Disadvantages
1. Poor absorption of macromolecules.
2. Entrapment of bubble during formulation

The formulation of emulgel includes aqueous phase, oil phase, emulsifying agent, gelling agent and penetration enhancers. The oil phase is generally used as a drug reservoir of hydrophobic drugs, whereas the aqueous phase is used for the swelling purpose of gelling agent. Water and alcohol are most commonly used as anaqueous phase. Emulsifiers are used to upholdthe stability of preparation during its shelf life and cause emulsification during manufacturing. e.g. polyethylene glycol 40 stearate, sorbitan monooleate (Span 80), polyoxyethylene sorbitan monooleate (Tween 80), stearic acid, sodium stearate. The most crucial ingredient of an emulgel is a gelling agent. It is utilized to improve the dosage forms consistency,e.g.carbopol 934, carbopol 940. The permeation enhancers partition into and interact with skin constituents to induce a

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temporary and reversible increase in skin permeabilityexample, oleic acid, menthol, clove oil, lecithin, isopropyl myristate, urea, linoleic acid, cinnamon, etc.

This review is focused on the application of emulgel in various conditions

1. For inflammation

Many papers are published on the use of emulgel in inflammation.Aceclofenacemulgelis prepared by carbopol 934 as a gelling agentand liquid paraffin as an oil phase.Gokani et al prepared aceclofenacemulgel by using linseed oil and carbomer 934.Penetration enhancers like menthol, clove oil,propylene glycoletc.,are used to enhance drug diffusion throughs.corneum. Carrageenan induced paw oedema and hot plate modelin Wistar rats are used to evaluatethe efficacy of emulgels.Kusuma preparedrutintrihydrateemulgel using liquid paraffin as oil and clove oil as a penetration enhancer and optimized the formulation through central composite design.Mahajan et al. prepared dexbiprofenemulgelby using oleic acid as oil phase and concluded that the optimized formulation is comparable with marketed diclofenac gel inanti-inflammatory activity.Burki et al. prepared dexibuprofen-capsaicin emulgel with mentha oil as permeation enhancer and reported that the cumulative amount of capsaicin permeated through rabbit skin was 9.83 ± 0.037 μg/cm^2 by use of 100 mgmenthol (as permeation enhancer), 7.23 ± 0.037 μg/cm^2 with 75 mg menthol, and 2.23 ± 0.061 μg/cm^2 without menthol after 6.5 h. The permeation of dexibuprofen was showed 19.53 ± 0.054 μg/cm^2, 13.87 ± 0.032 μg/cm^2, and 3.83 ± 0.074 μg/cm^2**.**Usha et al. (2020) prepared etoricoxibemulgel with carbopol and/or HPMC K4M and used clove oil, almond oil and olive oil as a penetration enhancer.The formulation prepared with the combination of carbopol and HPMC k4m and olive oil as penetration enhancersshowed a good release compared with others**.**Obanewa et al. prepared etoricoxib emulgel using the two forms ofa gelling agent likecarbopol 934 and HPMC K4M with emulsifiers like span 20 and tween 20. The etoricoxib emulgel formulation showed a substantial reduction of paw oedema thickness and volume at 8 hrs or more after carrageenan injection, demonstrating that the emulgel possesses fairly good anti-inflammatory activity. The anti-inflammatory effect of the formulation was compared with the standard marketed product of indomethacin.Coconut oil and HPMC K15M are used to prepare nimesulide emulgel.Wadher et al.selected Carbopol tween 20 and span 80 as independent variables to optimized nimesulide emulgel by 2^3full factorial design and ph, viscosity, spreadability and drug content as a response.Formulation containing carbopol (0.5g) span80 (1) and tween 20 (0.5) has shown maximum drug release.Chavda and Rupaparaformulated and evaluated an emulgel formulation of naproxen, a hydrophobic drug, using carbopol 934 as a gelling agent and two types of penetration enhancers, i.e., clove oil and methyl salicylate. Naproxen emulgel formulations prepared with carbopol 934 showed drug release, which remained unchanged upon storage for three months. However, the clove oil-based emulgel showed fluidity on three months of storage. Sri and Arjun prepared naproxen emulgel by using arachis oil for emulsion and carpool 940as gelling agent. Based on permeability (2.49 x 10-3 cm2 /h) and enhancement ratio (2.22),the formulation containing carbopol 940 (0.5%w/w) and arachis oil (10%w/w) is considered as optimized formulation, and this formulation showeda higher enhancement ratio than that of marketed gel.Tapentadol is a centrally acting drugthat is believed to act through a dual mechanism as an opioid receptor agonist and an inhibitor of norepinephrine reuptake, approved to treat moderate to severe pain in adults 18 years and older. Based on tapentadolsolubility study,Ambhore et al.selected light liquid paraffin, tween 20 and PEG 400 as oil, surfactant and cosurfactantfor construction of pseudo ternary phase diagramand concluded optimized formulation of emulgel showed a significant increase in drug release rate in vitro and ex vivo.Ambala et al. prepared ketoprofenemulgels with hydroxypropyl methylcellulose and carbopol 934 as gelling agents; liquid paraffin as oil phase; tween 20, span 80 as emulsifiers. The results show carbopol shown better results when compared to HPMC as a gelling agent. F3 formulation showed 98.46±2.05% drug release in 8h with good clarity and physical appearance at the time of drug release studies. T10% and T80% showed the values of best formulation F3 was found to be 0.9 h and 6.6 h, respectively. Indomethacin emulgel preparationxanthan and locust bean gumas a gelling agent, castor oil as oil, clove oil as a penetration enhancer, span 80 and tween 80 as an emulsifier is used by Joshi et al. and studied on an animal model in carrageenan-induced rat paw oedema on healthy albino mice. Resultingformulationemulgeldisplayed pH 6-6.7, viscosity 48400cps, good physical appearance, and

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drug content in the range of 98.82±1.24, spreadability in the range of 20.4±1.52, good extrudability, in vitro release 97.22% and possess a good anti-inflammatory activity. In vitro survey of ketoprofen release from emulgels were investigated by Peneva et al. emulgels prepared with different quantity of oil phase- 5 %, 6 %, 7.5 % light liquid paraffin (LLP) were researched, and for a gelling agent was used carbopol 940 and reported most suitable concentration of light liquid paraffin is 7.5 %. Archana et al. formulated theaceclofenac topical emulgels with utilize of different kinds of gelling agents: carbopol 940, carbopol 934, HPMC E15 cps, Na CMC, pluronic F-127 and HPMC K4 M using different concentrations compared by Archana et al. and reported that after use of topical emulgels with 8hrs release of drug (through dialysis membrane) could be successfully formulated in carbopol934, carbopol-940. So, these are selected as optimized formulations of topical aceclofenac. Anti-inflammatory tests were conducted onwistar albino male rats using the carrageenan-induced ratpaw oedema test. Mulyeet al. prepared Indomethacin emulgel using two types of gelling agents: carbopol 934 and xanthan gum, light liquid paraffin as oil phase, tween 80, span 80 as an emulsifier and optimized using a two factor, two-level factorial design. The studies found that xanthan gum based formulations showed more promising results, so natural gelling agent xanthan gum is a better gelling agent than synthetic gelling agent carbopol 934. Xanthan Gum consuming the oil phase concentration at its low level and emulsifying agent concentration at its high level was the formula of choice. The animal model right hind paw of the rats. Ketoprofenemulgelsis prepared with hydroxypropyl celluloses (HPC) and hydroxypropyl methyl celluloses (HPMC).The two polymers used as gelling agents and investigated the type and concentration of these on the release of ketoprofen and oleic acid, tween, carveol, terpene, and isopropyl alcohol were used as penetration enhancers. The effect of these enhancers on the diffusion of ketoprofen across the semi-permeable membrane was tested by Hosny et al.Results exposed that the emulgel formulations exhibited high drug release, especially at low polymer concentration was from a diffusion-controlled mechanism. The optimized formulation containsketoprofen 2%, HPC 2%, and 5% oleic acid, which exhibited improved anti-inflammatory activity compared to commercially available gel. The optimized formulation was tested for its anti-inflammatory activity on the carrageenan-induced rat paw oedema model. Results Topical emulgel enhanced permeation of ketoprofen and possed an effective anti-inflammatory activity, with avoidance of GIT adverse effect.Khullar et al. prepared mefenamic acid emulgel with carbapol 940 as a gelling agent. mentha oil and clove oil were utilized as penetration enhancers.Liquid paraffin as oil phase, tween 20 and span 20 as an emulsifier. From the in vitro studies, prepared formulation F4 showed a maximum release of 56.23% in 240 min. Ex vivo drug release was also performed in which prepared formulation F4 showed the best release of 56% in 240 min. The prepared formulations F2 and F4 were comparable with the marketed diclofenac topical gel. The animal model edema was induced on the left hind paw of the rats by subplantar injection of 1% (w/v) carrageenan. The carrageenan-induced paw oedema and hot plate testsrevealed anti-inflammatory and analgesic activity**.** Khuntet al.preparedpiroxicamemulgelformulation with carbompol 940 as a gelling agent, oleic acid as oil, tween-80 and span-80 as emulsifiers and propylene glycol and cetostearyl alcohol as co-surfactant by utilizing 3^2 full factorial designs to study the effect of independent variables, i.e. concentration of emulsifiers (X1) and carbomer (X2) on dependent variables like % drug release at 2 and 6 hours. The optimizedformulations contained a lower concentration of carbopol (0.5 %) and higher emulsifiers (6%). The optimized prepared formulation was evaluated for zeta Potential, viscosity, spreadability, skin permeation and stability. Skin permeation (%) of optimized batches (F3 and F12) in 24 hours was 87.89% and 89.09 %, respectively. The prepared formulation batch F12 had better anti-inflammatory activity than the marketed preparation. The animal model is paw oedema. Bhanu et al.inspected that the conventional diclofenac emulgel formulation contains isopropyl alcohol to increase the solubility of diclofenacdiethylamine. It is highly flammable may cause eye and cutaneous irritation. Prolonged skin contact with isopropyl alcohol may cause eczema and sensitivity. Bhanu's working hypothesis was to develop diclofenac emulgel without isopropyl alcohol and match the optimised formulation's in vitro and ex vivo permeability with the conventional formulation. Formulate the emulgel with carbomer 934p as a gelling agent, liquid paraffin as oil.

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2. For fungal infection

Fluconazole emulgel prepared with liquid paraffine and sesame oil was compared by Nailwal and reported that vegetable oil-based emulgel are stable and effective and can be used instead of liquid paraffin based emulgel. Patil et al. prepared fluconazole emulgel with liquid paraffin and Tween 20 and Span 20 as emulsifier and propylene glycol and methyl alcohol as co-surfactant and investigated the influence of the concentration of the gelling agent, emulsifying agent and oil phase on the drug release from prepared emulgel and reported that emulsifying agent concentration had the most obvious effect on the drug release from the emulgel followed by oil phase and finally the type of gelling agent.

Shankar et al. prepared luliconazoleemulgel with carbopol 934. They concluded that luliconazoleemulgel formulation prepared by using an emulsifying agent in its high level and liquid paraffin in its low level was the choice of formula since it showed the highest drug release and antifungal activity.

Tioconazole loaded emulgel containing carbopol 934 as a gelling agent, light liquid paraffin as oil, span 80 and tween 80 as emulsifiers were prepared by Sah et al. The results showed the spreadability in range of 6.6 to 8.833 cm and extrudabilityin the range 15.63 to 35.27 g/cm^2. The viscosity was in the range of 15240 to 56340 cps at 10 rpm and concluded that tioconazole emulgel provide a better platform for delivery of hydrophobic drug for topical route and so able to produce better patient compliance. Tolnaftate, an antifungal agent, has poor solubility and low permeability. Emulgel was formulated by preparing Tolnaftate emulsion and incorporated into carbopol-940 gel base with two different penetration enhancers, i.e. eucalyptus oil and transcutol at a concentration of 1%, 3% and 5% w/w separately. When assessed for antifungal activity, the zone of inhibition of formulation was significantly improved compared to a pure drug emulgel without eucalyptus oil. They attributed this to increased penetration of emulgel in fungi cells in the presence of eucalyptus oil, which translated into efficient antifungal activity.

Yassin et al. prepared clotrimazoleemulgel with carbopol 934 or hydroxyl propyl methyl cellulose 2910 as a gelling agent, liquid paraffin as oil, tween20, Span20 as emulsifiers. It was optimized using a 2^3 factorial design considering three independent factors at two levels. The selected factors were gelling agent (carbopol 934 and hydroxyl propyl methyl cellulose), liquid paraffin (2.5% and 5%) and emulsifying agent (1.5 and 2.5%). The amount of drug released and the antifungalactivity was chosen as two dependent responses. The prepared emulgel were also evaluated for their physical properties, pH, drug content and rheological properties. The study also shows that the use of 2 3 factorial designs are valid in predicting the optimized formulation, which was found to be HPMC-based emulgel with liquid paraffin in its low level and emulsifying agent in its high level since it shows the highest drug release and antifungal activity. Clotrimazoleemulgel prepared with the gelling agent (carbopol 934 and methylcellulose), the concentration of both the emulsifying agent (2% and 4% w/w of a mixture of span 20 and tween 20) and the oil phase (5% and 7.5% w/w of liquid paraffin) and the type of oil phase (liquid paraffin and cetyl alcohol), on the drug release from the prepared emulgels was investigated by Khalil etal. clotrimazoleemulgels exhibited higher drug release than canestin® cream. In vitro release showed that methyl cellulose-based emulgel gave better release than carbopol 934 – based one.Sabr et al. prepared miconazolenitrate emulgel with sodium carboxymethylcellulose (SCMC) and carboxypolymethylene (carbomer 941) as gelling agents gelling agent,liquid paraffin as oil and Span 20, Tween 20 as an emulsifier. In vitro release showed that SCMC emulgel bases gave better release than carbomer 941 bases and the release of drug increase from both bases to increase the concentration of emulsifying agent. Mohamed et al. prepared chlorphenesinemulgel with two types of gelling agents: hydroxypropylmethylcellulose (HPMC) and carbopol 934, liquid paraffin as oil, tween 20, span 20 as an emulsifier. The 2^3 factorial designs was employed to assess the concentration of both the oil phase and emulsifying agent and impact of the nature of the gelling agent on the drug release from the prepared emulgels. The HPMC-based emulgel with the liquid paraffin in its low level and the emulsifying agent in its high level proved to be the formula of choice since it showed the highest drug release and antifungal activity.

3. For bacterial infection

Srivastava et al. prepared fusidic acid emulgel with carbopol 934 as gelling agent, light liquid paraffin as oil, span 20 as emulsifier and propylene glycol as co-surfactant, peppermint oil as a penetration enhancer. From in vitro study, formulation shows a maximum release of 95.25%

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in 8 hours. Fusidic acid can be used as a steroidal bacteriostatic agent for topical drug delivery. Daood et al. prepared metronidazole as topical emulgel with carbopol 940 as gelling agent, liquid paraffin as oil, Span 20, Tween 20 as an emulsifier and report show drug release which deliver about 9% of drug within five hours.Oleic acid based ofloxacin emulgel prepared with carbopol-940 as gelling agent, tween-80 and span-80 as emulsifiers, propylene glycol as a humectant Liquid paraffin and oleic acid as oil was compared by Manaswitha et al. and reported that emulgel formulated with oleic acid exhibited greater flux when compared with those formulated with liquid paraffin. Baibhav et al. prepared clarithromycin emulgel with carbopol 934 as gelling agent, spans 80, tweens 80 as an emulsifier, light liquid paraffin as oil and optimized formulation showed the highest drug release and excellent antimicrobial activity when compared to the marketed azithromycin gel.

4. For Acne

Ranjan et al. prepared clindamycin phosphate emulgelwith carbopol 941 as a gelling agent, light liquid paraffin as oil, tween-20, span-20 as emulsifiers and propylene glycol as cosurfactantand reported that maximum drug release and anti-acne activity when compared to the marketed clindamycin gel. Thakur et al. prepared benzoyl peroxide emulgel with four different vegetable oils (almond oil, jojoba oil, sesame oil, and wheat germ oil)to utilize the emollient property of the oil. The idea was to overcome the skin irritation and dryness caused by benzoyl peroxide, making the formulation more tolerable. The optimized formulation with sesame oil (6%w/w), was found and the formulation also contains tween 20, span 60 as an emulsifier. The efficacy of anti-acne emulgel with 2.5% Thymus vulgaris L. was evaluated by using a camera with a specific UV-light to visualize the fluorescing porphyrins(Visiopor®PP34N) and Visioface®1000D (a full-face photographic analysis). Single-blind, randomized, split-face, placebo-controlled study was conducted. 25 patients with mild to moderate facial acne vulgaris was applied emulgel with Thymus vulgaris L. (TF) and placebo formulation (PF) twice daily on face for 90 days. A significant ($p < 0.05$) reduction in acne severity and other parameters was observed by applying TF. Collectively, formulation with 2.5% Thymus vulgaris L. could be an effective and well-tolerated medication to treat mild to moderate acne. Another anti-acne emulgel containing 20% green tea extract and 5% avocado oil was prepared and evaluated in twelve female subjects by using non-invasive skin bioengineering techniques. She reported that a cosmetically acceptable, stable, and effective emulgel with good hydrating properties for acne was prepared.

5. For Psoriasis

Apremilastemulgelprepared with carbopol 934 and xanthan gumwas compared by Ganarajan and reported that xanthan gum is a better gelling agent than synthetic gelling agent carbopol 934.The calcipotriol emulgel was prepared with carbopoland polyethylene glycol, Kollicream3C and KolliphorCS20 as emulsifiers. They reported that use of penetration enhancers, PEG and isopropyl alcohol couldimprove the penetration of the drug through the epidermis than calcipotriol ointment.Tretinoin emulgel was optimized using 3^2 response surface design and by changing ratios of excipients and using 3^2 optimal response surfaces design. The tretinoin emulgel was optimized on the basis tretinoin content and in vitro release profile of formulated emulgel batches. The in vitro anti-acne activity of optimized emulgelagainst Propionibacterium acne (P. acne) shown zone of inhibition of diameter 34.54±0.26mm which was found to be the comparatively same as that of marketed Sotret® gel (zone of inhibition 36.13±0.43mm).

II. CONCLUSION

At present, emulgel is one of the new technologies used for dual control release of emulsion and gel. Many drugs that have utility in treating skin disorders are hydrophobic and can be delivered through emulgel by incorporating in the oil phase of the emulsion. Since emulgel possesses an edge in spreadability, adhesion, viscosity and extrusion, they will become a popular drug delivery system.

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