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EMULGEL-NOVEL TOPICAL DRUG DELIVERY SYSTEM–A COMPREHENSIVE REVIEW

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ABSTRACT: Emulgel systems are currently of attention to the pharmaceutical scientists because of their substantial potential to act as drug delivery vehicle by incorporating a broad range of drug molecules. These are either emulsion of water in oil type or oil in water, which is gelled by mixing it with a gelling agent. Incorporation of emulsion into gel makes it a dual control release system & also increases its stability. Due to lack of insoluble excipients and excess oily bases, it demonstrates better drug release as compared to other topical drug delivery system. Due to nongreasy because of the presence of gel phase which favors good patient compliance. In order to understand the potential of emulgel as delivery vehicles, this review gives an overview of the ideal properties, formation, and characterization of emulgels. The use of emulgel -based systems as drug delivery vehicles is reviewed, with particular emphasis being placed on recent developments and future directions.

INTRODUCTION: The human being, since many ages get experienced with various types of diseases influencing their health and prosperity. The effort to cure diseases has been driving in the discovery of various medications, drug and delivery systems. To get a remedial response of drug required for treatment of illness different routes of administration are taken after. Route of administration depends on sort and seriousness of the disease. For skin disorders, the topical route is generally favored. Topical drug delivery systems are such system in which direct application of a formulation containing an active pharmaceutical ingredient to the skin to obtain the localizing effect of drug.¹

Topical drug delivery system has several advantages such as the ability to deliver drug more selectively to a specific site and prevention of incompatibility associated with gastro-intestinal.² Moreover, topical deliveries by avoiding first pass metabolism provide an increased bioavailability and consistent delivery for an extended period.^{3,4} In topical drug delivery system, drug reaches to the site of action via diffuses out of the delivery system and their absorption takes the place of the skin.⁵ Percutaneous absorption can be improved by increasing the release rate of the drug from dosage form.⁶ The release rates of medications from topical preparations depend straightforwardly on various physical, chemical properties of the carrier and the medication utilized.^{7,8}

Since the mid-1980s, emulsion gels have been picking up significance in pharmaceutical topical semisolid dosage forms. Their wide usage as pharmaceutical dosage form originates from the wide use of emulsion systems, especially for dermatological formulae.

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Emulgel are emulsions, either of the water-in-oil or oil-in-water type, which are gelled by mixing with a gelling agent.⁹ The emulsion also acts as controlled release drug delivery system in which drug particles entrapped in internal phase go through the external phase to the skin and slowly get absorbed. The drug reaches the external phase of the skin in a controlled manner through the internal phases which act as a reservoir of the drug. Gel captures small drug particles and provides its release in a controlled manner because of a cross-linked network. It prolongs the contact period of medication over the skin because of its mucoadhesive property.¹⁰ Since Emulgel possesses the property of both gel and emulsions it acts as dual control release system.¹¹ Water-in-oil emulsions are employed more extensively for emollient actions and for the treatment of dry skin and emollient applications while oil-in-water emulsions are most useful in general cosmetic acts as a water washable drug bases.¹²⁻¹⁴

When emulsion possesses the property of thixotropic then the processes of penetration into the skin are simplified. Hence to improve emulsion penetration and stability it is incorporated into the gel. Further, gels for dermatological use have a few positive properties, for example, being emollient^{15, 16}, greaseless, thixotropic, easily removable, nonstaining and compatible with various excipients. Release rate, as well as the stability of incorporated drug, can be affected by type and concentration of polymer which form the gel. Emulgels have good patient acceptability. It can be suitably applied to the skin due to its non-greasy nature in comparison to other topical formulations such as ointments, creams etc. which are very much thick and require excess rubbing.¹⁷⁻²⁰ Emulgels may serve as a better option when one is concerned with the topical delivery of poorly water soluble drug. It has also proven better and a stable vehicle for poorly water-soluble or hydrophobic drugs.²¹⁻²³

TABLE 1: IDEAL PROPERTIES OF DRUG CANDIDATE TO FORMULATE AS EMULGEL²⁴

S. No.	Drug Candidate
1	Drug dose should be low i.e. less than 10 mg
2	Molecular weight of drug should be 400 Dalton or less
3	Half life of drug 10 hr or less
4	Partition coefficient i.e. Log p (Octanol-water) between 0.4-0.8
5	Having a skin permeability coefficient more than $0.5 \times 10^{-3} \frac{cm}{hr}$
6	Oral bioavailability and therapeutic index should be low.
7	Drug should be non irritating and non-sensitizer having a less polarity

2. Various ingredients of Emulgel formulation:

2.1 Aqueous material: This forms aqueous phase of the emulsion. Generally, water is used.

2.2 Oils: They are responsible for the oily phase of the emulsion. The oil phase has great importance in the formulation of emulsion /microemulsion/ nanoemulsion as physicochemical properties of oil (e.g., molecular volume, polarity, and viscosity) significantly govern the spontaneity of the emulsification /micro- emulsification / nano emulsification process, the droplet size of the respective emulsion, drug solubility. Usually, the oil, which has the maximum solubilizing potential for the selected drug candidate, is preferred as an oily phase for the formulation of emulsion/ microemulsion/nanoemulsion. This helps to attain the maximal drug loading. Hence, the choice of the oily phase is often a compromise between its tendency to solubilize the drug and its capability to

facilitate the formation of the respective emulsion with desired characteristics. Oil phases which are used in development of emulgel are balsam oil,²⁵ birch oil,²⁶ castor oil,²⁷⁻²⁹ isopropyl myristate,³⁰⁻³² myrrh oil,³³ rose hip oil,³⁴⁻³⁵ wheat germ oil.³⁶⁻³⁸

2.3 Emulsifiers: Emulsifiers are used to control emulsification process and stability. By incorporating an appropriate emulsifying agent stability of emulsion can be increased because these are thermodynamically unstable. Surfactants having HLB values greater than 8 such as the nonionic surfactant (spans, tweens) are used in the formulation of o/w emulsions whereas mineral oils such as liquid paraffin have HLB value less than 8 and therefore are used in the formulation of water in oil emulsions. In comparison to the individual system of span or tween, mixtures of span 20 and tween 20 results greater stability of the emulsion.³⁹

2.4 Permeation enhancer: Penetration enhancers are the substances that assist the absorption of penetrant through the skin by temporarily thinning the impermeability of the skin. Ideally, these materials should be pharmacologically inert, nonirritating, nontoxic, and compatible with the excipients and drugs, colorless, odorless, tasteless, and inexpensive and have good solvent properties. The enhancer should not guide to the loss of body fluids, electrolytes, and other endogenous materials, and skin on its removal should immediately regain its barrier properties. Various penetration enhancers used in the emulgel formulation are oleic acid,⁴⁰ clove oil⁴¹ and menthol⁴² etc.

2.5 Gelling Agents: Gelling agents are used to forming gel base which by incorporating emulsion

to form emulgel. These are also known as thickening agents which expand the consistency of any dosage form by swelling in the aqueous phase and forming gelly like structure.⁴³ Incorporation of gelling agent to a system makes it thixotropic.⁴⁴

HPMC based Emulgel was found to be superior to Carbopol based Emulgel since it showed better drug release rate NaCMC based Emulgels for vaginal application since it showed higher mucoadhesivity which increased drug residence time and also best *in-vitro* and *in-vivo* performance. HEC based Emulgel showed low mucoadhesion but good drug release profiles and rheological characteristics. Pemulen based Emulgel meant for buccal administration.

TABLE 2: VARIOUS GELLING AGENTS USED IN PHARMACEUTICAL DOSAGE FORMS

S.no	Gelling agents	Concentration used (%w/w)	Pharmaceutical adaptability	Active pharmaceutical ingredient	References
1	Sodium CMC	3-4%	stand autoclaving hence suitable for sterile gels	Benzydamine	45
2	Carbopol-934	1%	Provide controlled release of API incorporated	Chlorphenesin	46
3	Carbopol-940	1%	Because of high viscous gel, provide controlled release of API incorporated	Mefenamic acid	47
4	HPMC	2.5%	Having good stability, microbial resistance,	Clorphenesin	48
5	Combination of HPMC & Carbopol	1.2%	Combination improve stability	Ketorolac, clotrimazole	49-50
6	Pluronic® F127	1-3%	Good clarity and better solubility in cold water	Piroxicam	51
7	Pemulen	0.1-0.4%	Provide rapid release of oil phase, excellent stability	Flurbiprofen	52

3. Formulation of emulgel:⁵³⁻⁵⁴

Step1: Preparation of gel using the gelling agent: Sufficient quantity of Carbopol 940 (1% w/w) was weighed and sprinkled onto warm distilled water with continuous stirring. The dispersion was allowed to hydrate for 1-2 hours. Other ingredients like propylene glycol (10 % w/w) and glycerol (10 % w/w) were added subsequently to the aqueous dispersion with continuous stirring. A required quantity of drug (1 % w/w) was added and properly dispersed. The dispersion was neutralized to pH 6 using triethanolamine and the final weight was adjusted with distilled water. The gel was sonicated for 15 minutes and kept overnight to remove air bubbles.

Step 2: Preparation of Emulsion: Depending upon whether oil in water or water in oil emulsion was formulated.

Step 3: Incorporation of the emulsion into gel base: Finally emulsion was incorporated in gel base to form emulgel.

4. Characterization of Emulgel:

4.1 Physical appearance: The prepared emulgel is inspected for the colour, homogeneity, consistency.⁵⁵

4.2 pH: The pH values of 1% aqueous solutions of the prepared gels were measured by a digital pH

meter. Electrodes were completely dipped into the semisolid formulations and pH was noted.⁵⁶

4.3 Spreadability: To study the spreadability of formulations, special apparatus was designed. Spreadability is expressed in terms of time in seconds taken by two slides to slip off from formulations, placed between, under the application of a certain load lesser the time is taken for the separation of the two slides, better spreadability. Two glass slides of 6x2 cm each were selected. The formulation was placed over one of the slides whose spreadability had to be determined (500mg). This slide was placed over the other slide in such a way such that formulation was sandwiched between the two slides. The formulation between the two slides was squeezed consistently to frame a slight layer, for this reason, weight (100 gm) was set upon the upper slide. The excess of the formulation adhering to the slides was scrapped off after the weight was removed. The lower slide was fixed on the surface of the apparatus and the upper slide was tied to a string. To this sting load (20 gm) could be applied with the help of a simple pulley. Under the direction of weight applied the time taken for the upper slide to move the distance i.e of 6cm and separate away from the other slide(lower) was noted. The experiment was repeated (n=3) and the average of such determinations was calculated for each formulation

$$\text{Spreadability} = \frac{M}{T} L$$

Where, M= Weight which is tied to the upper slide (20gm)

L= Length taken of glass slide (6cm)

T= Time taken (seconds)

The delivery of the correct dose of the drug depends highly on the spreadability of the formulation.⁵⁷

4.4 Swelling Index: For determination of swelling index of formulated emulgel following procedure adopted, 1 gm of the gel is taken on porous aluminum foil and then placed separately in a beaker of 50 ml containing 10 ml 0.1 N NaOH. Then samples were taken from beakers at different time points and put it on a dry place for some time after it reweighed. Swelling index is calculated as follows:

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

Where,

Wo = Initial weight of emulgel at zero time

Wt = Weight of swollen emulgel after time t

(SW) % = Percent swelling Index⁵⁸

4.5 Extrudability study of topical emulgel (Tube Test): It is a typical experimental test to measure the force required to expel the material from the tube. The formulation, whose extrudability checked, filled in clean, lacquered aluminum collapsible metal tubes. The tubes were pressed by the help of finger to extrude the material. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in the percentage of emulgel. Emulgel extruded from lacquered aluminum collapsible tube on the application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds.⁵⁹ The experiment was repeated (n=3) and the average of such determinations was calculated for each formulation:

$$\text{Extrudability} = \frac{\text{Weight applied to extrude emulgel from tube (gm)}}{\text{Area (cm}^2\text{)}}$$

4.6 Bio-adhesive strength measurement: A modified balance method was using for bioadhesion measurement. The two pans were removed from physical balance. On the left side, a glass slide was hanged and a 100 ml beaker was used in place of right side pan. A weight of 20 g was hanged on the left side, for balancing the assembly. Another glass slide was placed below the hanged slide. On both slides, portions of hairless fresh rat skin were attached. One gram of gel was placed between two rat skin faces. To form bioadhesion bond, a little pressure was applied, and then slowly water was added to right side beaker, till the gel was separated from one face of rat skin attached. The volume of water added was converted to mass. This gave the bioadhesive strength of gel in grams.⁶⁰

4.7 Drug Content Determination: Gel formulation (1 gram) was dissolved in suitable solvent. Filtered it to obtain clear solution. The resulting solution absorbance was noted using UV Visible spectrophotometer. Drug content was determined from calibration curve for drug.⁶¹

4.8 In-vitro drug release studies *In-vitro* release behaviour of the drug from emulgel formulations were investigated using egg shell membrane. An interesting investigation used egg membrane which, like human stratum corneum, consists mainly of keratin.⁶² By using 0.5M hydrochloric outer shell of the whole egg was dissolved which resulting in a membrane. Thereafter, the contents of the egg may be detached and the membrane washed and refrigerated or soaked in isopropyl myristate under vacuum to impregnate the keratin matrix. The replacement of water in the membrane with this lipid is assumed to increase its likeness to stratum corneum biochemistry. The Keshary-chien cell was used for release and permeation study. One gram of gel was applied on 9.8 cm² area of the surface of egg membrane tied to the lower end of donor compartment. The volume of the receptor fluid was reserved 37.5 ml.

The temperature condition of the receptor fluid maintained at 37° C and stirred continuously at 100 rpm on a magnetic stirrer. Aliquots of 3.0 ml were withdrawn and analyzed for the drug content after suitable dilutions by spectrophotometric method. The volume of fluid which was withdrawn for analysis be replaced with the same volume of the fresh buffer after each sampling. The cumulative amount released across the egg membrane was calculated and plotted against time. The best batches showing high percent release were selected further for *ex-vivo* studies using rat skin.

4.9 Ex-vivo skin permeation and retention studies: Albino rat 10-12 weeks old weighing 200-250 g was used. The excised skin was placed in aluminum foil the dermal side of the skin was delicately teased off for any following fat and/or subcutaneous tissue. The skin was then precisely checked through an magnifying glass to guarantee that specimens were free from any surface inconsistencies, for example, small openings or cervices in the part that was utilized for transdermal permeation studies. The skin was washed with physiological buffer saline and freshly obtained skin was used in all experiments.

The *ex-vivo* skin permeation of drug from different formulations was studied using Keshary-chien cell. The effective permeation area of the diffusion cell

was 9.8 cm². The receptor compartment has a volume of 37.5 ml. Albino rat skin was sandwiched securely between donor and receptor compartment with the donor compartment having epidermis site. The donor compartment was maintained at 37±1°C with constant stirring. The emulgel formulation was applied to the epidermal surface of the rat skin. At predetermined time interval for 24 hr (0.5hr, 1hr, 2hr, 4hr, 6hr, 8hr, and 24hr), 3.0 ml of aliquots were withdrawn and were replaced with an equal volume of fresh receptor compartment solvent to ensure sink condition. The cumulative percentage drug diffused across the skin was calculated at each sampling point.

The amount of free drug content in the receptor compartment and the amount of drug remained on the epidermal surface of the skin on subtraction from the initial drug content of the formulation applied resulted the amount of drug content in the skin. The *ex-vivo* permeation study of emulgel is compared with the marketed emulgel for permeation characteristics. All the determinations were carried out in triplicate and the data were compared by ANOVA.

4.10 Stability Studies: The optimized emulgel formulation was selected for stability study. Sufficient quantity of emulgel formulation was sealed in 10 gm collapsible tube in triplicate, and subjected to stability studies at 5°C, 25°C, /60%RH, 30°C 65%RH and 40°C/ 75%RH for a period of 3 months. The samples were analyzed at predetermined time intervals for pH, physical appearance, rheological properties and drug content.⁶³

4.11 Kinetics Modeling: Data obtained from *ex-vivo* permeation studies were fitted into zero order, first order, Higuchi, and mathematical models for evaluation of drug release kinetics. The model for best fit was predicted from the value of R². For an ideal fit, value of R² i.e. higher, the value of R² best was the model fitted. Hence, the model which gives the R² value nearest to 1 describes the best order of drug release.⁶⁴

TABLE: 3 CURRENT ELEVATIONS IN DEVELOPMENT OF EMULGEL FOR VARIOUS DRUGS

Drug	Aim	Use	References
Amphotericin B	Evaluation of the <i>in vivo</i> leishmanicidal activity of amphotericin B emulgel: An alternative for the treatment of skin leishmaniasis	Leishmaniasis therapy	65
Metronidazole and ciprofloxacin	Groundnut oil based emulsion gels for passive and iontophoretic delivery of therapeutics	Passive and iontophoretic delivery of therapeutics	66
Amlodipine besylate	Preparation of amlodipine besylate emulgels for transdermal administration and its percutaneous permeability <i>in vitro</i>	Transdermal delivery	67
Acyclovir and ketoconazole	Topical delivery of acyclovir and ketoconazole	Viral and fungal cutaneous manifestations	68
Lacidipine	Novel non-ionic surfactant proniosomes for transdermal delivery of lacidipine: optimization using 23 factorial design and <i>in vivo</i> evaluation in rabbits	Antihypertensive	69
Pravastatin	Optimised transdermal delivery of pravastatin		70
Ciprofloxacin	Genipin-Crosslinked Gelatin-Based Emulgels: an Insight into the Thermal, Mechanical, and Electrical Studies		71
Diclofenac sodium	Evaluation of skin penetration of diclofenac from a novel topical non aqueous solution: A comparative bioavailability study	Pain relief	72
Diclofenac sodium	Nanoemulsion-based gel formulation of diclofenac diethylamine: design, optimization, rheological behavior and <i>in vitro</i> diffusion studies	Management of pain	73
Pinhão starch	Pinhão starch and coat extract as new natural cosmetic ingredients: Topical formulation stability and sensory analysis	Antioxidant activity	74
Terpinen-4-ol	The effect of rheological behavior and microstructure of the emulgels on the release and permeation profiles of Terpinen-4-ol	Antimicrobial properties	75
Betamethasone dipropionate	Development of a topical ointment of betamethasone dipropionate loaded nanostructured lipid carrier	For the treatment of atopic dermatitis	76
LEVORAG® Emulgel : Hibiscus esculentus extract, Carboxymethyl beta-glucan Dimethicone, glycerine, prunus amygdalus dulcis oil, borago officinalis seed oil Malva sylvestris extract, calendula officinalis extract, glycyrrhiza glabra extract	Prospective multicenter observational trial on the safety and efficacy of LEVORAG® Emulgel in the treatment of acute and chronic anal fissure	For treatment of acute and chronic anal fissure	77
Cyclosporin A	Formulation and evaluation of Cyclosporin A emulgel for ocular delivery	Topical ocular delivery	78
Meloxicam	Formulation and characterisation of Meloxicam loaded emulgel for topical application	Anti-inflammatory	79
Nimorazole	Preparation and evaluation of Radiosensitizing agent Nimorazole in topical emulgel	hypoxic cell radiosensitizing agent	80
Ketoprofen	Formulation development, <i>in vitro</i> and <i>in vivo</i> evaluation of microemulsion-based gel loaded with ketoprofen	Anti-inflammatory	81
Calcipotriol	Calcipotriol delivery into the skin as emulgel for effective permeation	In treatment of Psoriasis.	82
Allopurinol	Design and development of allopurinol emulgel		83
Terbinafine hydrochloride	Formulation, development and <i>in-vitro</i> evaluation of Terbinafine hydrochloride emulgel for topical	In treatment of fungal infection	84

	fungal infection		
Silver sulfadiazine	Development and characterization of silver sulfadiazine emulgel for topical drug delivery	Antimicrobial activity	85
Piroxicam	Effects of various penetration enhancers on percutaneous absorption of piroxicam from emulgels	Anti-inflammatory	86
Ketorolac Tromethamine	The enhancement of transdermal permeability of water soluble drug by niosome-emulgel combination	Anti-inflammatory	87

5. Various marketed Emulgel formulation:

Emulgel are commercially available in markets; some preparations of which are listed as following in Table. Voltaren Emulgel is a topical analgesic gel that provides relief in shoulder pain, back pain and reduces swelling. Voltaren Emulgel is non-greasy, white pleasant-smelling gel which is available in a 100g tube having a active ingredient diclofenac sodium 1% w/w (as diclofenac

diethylamine). Another emulgel is Diclomax Emulgel which is used in treatment inflammation of the tendons, ligaments, muscles and joint and manufactured by Torrent Pharma. Miconaz H emulgel which is manufactured by medical union pharmaceuticals having active ingredient miconazole nitrate and hydrocortisone posses bactericidal, fungicidal, anti-inflammatory and antipruriginous properties.

TABLE 4: VARIOUS MARKETED EMULGEL FORMULATIONS

Marketed formulation	API	Manufacturer	Use
Voltarol 1.16% emulgel	Diclofenac sodium	Novartis	Antiinflammatory
DiclomaxEmulgel	Diclofenac sodium	Torentpharma	Antiinflammatory
Miconaz-H-emulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals	Topical corticosteroid and antifungal

6. Future prospective: During formulation & development of any new formulation the most common problems faced from hydrophobic behavior of drugs which leads to poor water solubility and bioavailability problems. Because of hydrophobic nature of many drugs delivery of these to the biological system have be challenging. Creams, ointments and lotion are of different types of drug delivery system which has been applied topically have excellent emollient properties but retards the release of drugs due to presence of oleaginous bases. As compared to other topical systems gel provides quicker release of drug because gel provides aqueous environment to drugs. Hydrophobic drug can be incorporated in oily base and delivered to skin by using emulgel. All such points of interest of Emulgel over other topical drug delivery systems make them more effective and profitable. In future these properties will be utilized to convey more number of topical medications as Emulgel.

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