AMERICAN JOURNAL OF PHARMTECH RESEARCH
**Journal home page:** http://www.ajptr.com/

# Emulgel: A Novel Approach For Hydrophobic Drugs

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## ABSTRACT

The topical drug delivery facilitates a direct entry into the skin as a vital organ for diagnosis and cure without any threat of passing through first pass metabolism. Emulgels are nothing but, the combination of emulsion and gel. Emulgel is one of the novel strategy widely employed in acne, fungal infection, arthritis, inflammation, psoriasis and other topical infections. Emulgel for dermatological use has several constructive properties such as being thixotropic, emollient, easily spreadable, easily washable, greaseless, non-staining, water-soluble, greater shelf life, bio-friendly, clear and pleasant appearance. Emulgel is emulsion, either of water in oil or oil in water type, which are gelled by mixing with gelling agent such as HPMC, carbopol etc. However, gels carry a drawback in delivery of hydrophobic drug moiety and thus emulgel can prove a novel topical drug delivery for hydrophobic drugs by incorporating hydrophobic drug into gels using o/w emulsions. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then dispersion of oil globules in aqueous phase as a continuous phase, resulting in o/w emulsion and this emulsion can be incorporate into gel base.

**Keywords:** Emulgel, hydrophobic drugs, gelling agents, topical drug delivery.

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Received 13 March 2018, Accepted 28 March 2019

Please cite this article as: Mohite SV *et al.*, Emulgel: A Novel Approach For Hydrophobic Drugs . American Journal of PharmTech Research 2019.

# INTRODUCTION

Emulgels are the combination of emulsions and gels. [1] Emulsion, either of oil in water or water in oil type, which are gelled by mixing with a gelling agent such as carbopol , hydroxyl propyl methyl cellulose (HPMC), carboxy methoxy cellulose (CMC) etc.[2] Direct (oil-in-water) system is used to entrap hydrophobic drugs whereas hydrophilic drugs are encapsulated in the reverse (water-in-oil) system. Emulgel acts as dual control of drug release from the formulation, due to presence of both aqueous and non-aqueous phase.[3] Emulgels are preparations widely used for delivery of drug through skin. Its function in dermatology is realized mainly due to the advantages such as easy incorporation of hydrophobic drugs, thixotropy, greaseless, easily spreadable, and easy removable, emollient, non-staining, water-soluble, biocompatibility with greater shelf life and pleasant appearance.[4]

The U.S.P. defines gels as a semisolid system containing either suspension made up of either large organic molecule or small inorganic particle enclosing and interpenetrated by liquid.[5]Gel formulations generally show better drug release than ointments and creams. Inspite of many advantages of emulsions and gels a major disadvantage is their inability to delivery of hydrophobic drugs and instability during storage respectively. Such types of problems are overcome by using emulsion based approach that is emulgel preparations and thereby hydrophobic drug is successfully incorporated and enjoy the unique property of gels.[6]

**Factors affecting on skin penetration [7-9]**

The penetration of substances through the skin depends upon different factors:

**Age**

penetration is more in infant and children than in adults.

**Skin condition**

penetration is more on abraded or injured skin surfaces. Chemicals may cause wound and enhance diffusion.

**Hydration of the skin**

penetration is more in hydrated skin than dry skin. Hydration increases the permeability of the stratum corneum. Water is an useful penetration enhancer. Fat content of the epidermis has no much effect on penetration.

**Type of vehicles**

vehicles may possibly enhance penetration and absorption of the drug from the membrane surface. This depends on the kind of vehicle and the condition of the skin. Certain vehicles that may

possibly cause injury to the skin even minimal injury predispose to extra penetration of the drugs or other materials applied topically to the skin surface.

**Hyperemia**

vasodilatation of the blood vessels in response to different stimuli either local or generalized increases the diffusion. pharmacological and Physiological factors, the diffusion in vivo of topically applied substances be able to assessed by physiological or pharmacological signs or analyzed through chemical or histological techniques:

Vasoconstriction has been used for corticosteroids.

Vasodilatation for nicotinates.

Whealing for histamines.

Sweating for pilocarpine.

Anesthesia intended for local anesthetics.

**Lipoid soluble substances**

Facilitate diffusion of substances applied to the membrane surface. Steroid hormones and vitamin D, salts such as chloride and sulfate be capable of penetrate the skin surface. Gases and volatile substances be able to pass through the membrane.

**Factors to be considered when choosing a topical preparation** [10, 11]

1. Effect of the vehicle e.g. an occlusive vehicle enhances penetration of the active component and improves effectiveness. The vehicle itself may possibly have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the site. (e.g., gel or lotion for hairy areas)
3. Match the type of preparation with the type of lesions. For e.g., avoid greasy ointments for sensitive dermatitis.
4. Irritation or sensitization potential. Ointments and w/o creams are less irritating to skin while gels are irritating to skin. Ointments do not contain emulsifiers or preservatives if allergic reaction to these agents is a concern.

**Formulation considerations** [12]

The challenges in formulating topical emulgels are:

1. Determining systems that are non-toxic, non-comedogenic, non-irritating and non sensitizing.
2. Formulating cosmetically elegant emulgel.
3. The emulgel formulation must have low allergic potential, high biocompatibility and good physiological compatibility.

**Advantages of emulgels [13-15]**

1. Avoidance of the systemic adverse effects of drug i.e. first pass metabolism in the body.
2. Gastrointestinal incompatibility is minimized or prevented.
3. Improve patient compliance and acceptability.
4. Suitable for self-medication.
5. Provide target drug delivery on the body.
6. Site specific drug delivery.
7. Ability to easily terminate medication when needed.
8. Can easily pass through skin having dual behavior i.e. hydrophobic as well as hydrophilic.
9. They are suitable to apply on hairy skin due to absence of greasiness and lack of residues upon application.
10. Better stability and release of drug.
11. Better loading capacity.
12. Production possibility and low preparation cost.
13. No intensive sonication required.
14. Emulgels can be used to prolong the effect of drugs having shorter half life.

**Disadvantages of emulgels [16-17]**

1. Skin irritation on contact dermatitis may occur due to the drug or excipients.
2. Poor permeability of some drugs through the skin.
3. Chances of allergenic reactions.
4. Bubbles formed during emulgel formulation.
5. Drugs having large particle size (>400 Daltons) are not easily absorb or cross through the skin barrier.
6. Enzyme in epidermis may denature the drugs.[18]

**Types of emulgel**

**Macroemulsions gel**

These are most common type of emulgel where the particle size of droplets of emulsion is more than 400nm. Macroemulsion are thermodynamically unstable, but can be stabilized using surface active agents.[19] e.g. emulgel of mefenamic acid was prepared using carbopol 940 as gelling agent. Clove oil and mentha oil was used as penetration enhancer. Liquid paraffin was used as oil phase.[20]

**Nanoemulgel**

When nanoemulsion is incorporated into gel it is called as nanoemulgel. Nanoemulsions are thermodynamically stable, transparent (translucent) dispersions of oil and water which stabilized by an interfacial film of surfactant and co-surfactant molecules having a droplet size of less than 100 nm. e.g. carvedilol nanoemulgel was prepared using oleic acid and isopropyl myristate (3:1) as oil phase. Carbopol 934 was used as gelling agent. Carbitol and tween 20 were used as co-surfactant and surfactant respectively.[21]

**Microemulsion**

Microemulsions are transparent and thermodynamically stable as their droplet size range from 10 to 100 nm and they do not coalesce. e.g. microemulsion based clotrimazole vaginal gel was prepared using capryol 90 as oil phase and cremophor EL as surfactant. Carbopol ETD 2020 is used as gelling agent.[22]

**Important constituents of emulgel preparation**

**Aqueous Material**

Aqueous materials are required for the preparation of aqueous phase of emulsion.[23] Commonly used agents are water and alcohols.[24]

**Oils**

For the preparation of oily phase of emulgel, oily materials are required. Intended for externally applied emulsions mineral oils, either alone or combined with hard or soft paraffin. It workings both as the vehicle for the medicine and for their occlusive and sensory characteristics. Commonly used oils in oral formulations are non-biodegradable mineral and castor oils that provide a local laxative effect, and fish liver oils or various fixed oils of vegetable origin (e.g. arachis oil, cottonseed oil, and maize oil) are used as nutritional supplements.[25] Oils extracted from different types of plant with various medicinal values can be employed in emulgel formulation. Hiba et al (2016) carried one such research work using myrtle oil as oil phase for emulgel. Such emulgel containing myrtle oil as an antimicrobial agent for the treatment of human skin diseases. The other examples include almond oil, wheat germ oil, sesame oil.[26]

**Emulsifiers**

The inclusion of emulsifying agents are necessary to facilitate emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously formulated emulsions to months or years for commercial preparations e.g. polyethylene glycol 40, stearate, sorbitan mono-oleate (span 80), polyoxyethylene sorbitan monooleate (tween 80), stearic acid and sodium stearate.[27]

**Gelling Agent**

These are used to increase the consistency of any dosage form. These can also be used as thickening agent.[28] Table 1: Gelling Agents

**Table 1 : Gelling Agents**

| Gelling agents | Percentage on anhydrous basis | Dosage form |
|---|---|---|
| Carbopol 940 | 1% | Emulgel |
| Carbopol 934 | 1% | Emulgel |
| HPMC 2910 | 2.5% | Emulgel |
| HPMC | 3.5% | Gel |
| Sodium CMC | 1% | Gel |

If the concentration of gelling agent increases then extent of drug release is also increases. [29]

**Permeation Enhancers**

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability. Table 2: Penetration Enhancer

Other examples of penetration enhancers are pyrrolidones, eucalyptus oil, dimethyl sulphoxides, chenopodium oil etc.[30]

**Table : 2 Penetration Enhancer**

| Penetration enhancer | Percentage on anhydrous basis | Dosage form |
|---|---|---|
| Menthol | 5% | Emulgel |
| Clove oil | 5% | Emulgel |
| Lecithin | 5% | Gel |
| Oleic acid | 1% | Gel |
| Urea | 10% | Gel |
| Isopropyl myristate | 5% | Gel |
| Linoleic acid | 5% | Gel |

**Preparation of emulgel**

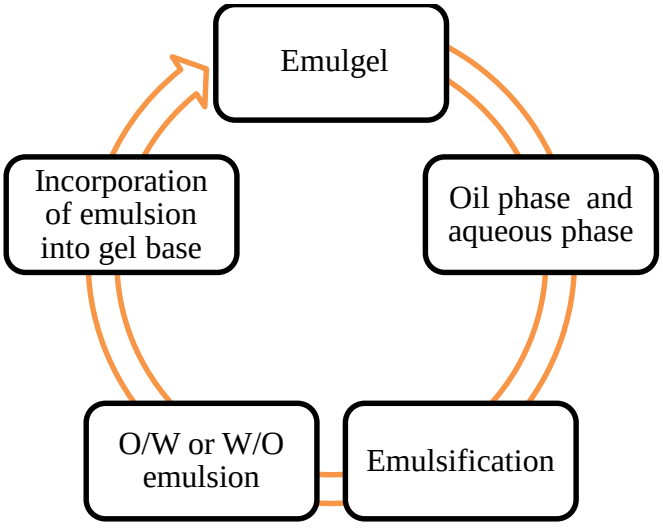


**Figure: 1 Flow diagram of Emulgel formulation [31-32]**

**Evaluation parameters**

**Physical examination**

The prepared emulgel formulations are analyzed visually for their color, appearance, homogeneity, consistency, grittiness and phase separation.[33-34]

**Spreadability**

Spreadability is determined by apparatus which consists of a wooden block, which is attached to a pulley at one end. Spreading coefficient is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on the wooden block. About 1 gm of prepared emulgel is placed on this ground slide. The emulgel preparation is then squeezed between this slide and second glass slide having same dimension as that of the fixed ground slide. The another second glass slide is attached with the hook. Weight of 100 g is placed on the top of the two slides for 5 min to expel air and to offer a homogenous film of the emulgel between the two slides. Measured quantity of weight is placed in the pan attached to the pulley with the help of hook.[35] Spreadability is expressed in terms of time in seconds taken by two slides to slip off from emulgel and placed in between the slides under the direction of certain load. A shorter interval indicates better spreading coefficient. It is calculated by using the formula [36]

$S = M. L / T$

Where M = weight tied to upper slide

L = length of glass slides.

T = time taken to detach the slides

**Extrudability study**

It is a typical experimental test to measure the force required to expel the material from the tube. It is based upon the determination of weight required to extrude 0.5 cm ribbon of emulgel formulation in 10 seconds from lacquered collapsible aluminium tube. More quantity extruded better is extrudability. The test is performed in triplicate and average value is calculated. The formula used to calculate extrudability is as follows: [37-38]

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

**Rhelogical studies**

The rheological property of the different emulgel formulations is determined at $25^0$C using a Brookfield viscometer with spindle no.18 at 100 rpm.[39]

**Swelling Index**

The swelling index of prepared topical emulgel is performed by taking weighed 1 gm of gel on porous aluminum foil and then placed separately undisturbed in a glass beaker of 50 ml contain 10

ml of 0.1 N NaOH. Then at different time intervals the samples are removed from beakers and put it on dry place for some time after it reweighed. Swelling index was calculated by using formula as follows: [40]

**SW % = [Wt – Wo / Wo] × 100**

Where, SW % = Equilibrium percent swelling,

Wt = Weight of the swollen emulgel after time t,

Wo = Initial weight of emulgel at time zero.

**Bio adhesive strength measurement**

The method is used for the measurement of bioadhesive strength. The fresh skin is cut into pieces and washed with 0.1N NaOH. Two pieces of skin were tied to the two glass slide separately from that one glass slide is fixed on the wooden piece and other piece is tied with the balance on right hand side. The left and right pans were balanced by adding extra weight on the left-hand pan. 1 gm of topical emulgel is placed between these two slides containing hairless skin pieces, and extra weight from the left pan is removed to sandwich the two pieces of skin and some pressure is applied to remove the presence of air. The balance is kept in this position for 5 minutes. Weight is added slowly at 200 mg /min to the left-hand pan until the patch detached from the skin surface. The weight (gram force) required to detach the emulgel from the skin surface gave the measure of bioadhesive strength. The Bioadhesive strength is calculated by using following: [41]

**Bioadhesive Strength = Weight required (in gm) /Area (cm2)**

**Drug content study**

Drug content study is carried out to determine the amount of the drug present in the certain quantity of the formulation. About 1 g of the emulgel is accurately weighed and transferred into 10 ml volumetric flask to which about 1 ml methanol is added, after vigorous shaking the volume made upto 10 ml with phosphate buffer pH 7.4. The volumetric flask is kept for 2 hrs and shaking is carried out in a shaker to mix it properly. The solution is passed through the filter paper and then absorbance is measured by using UV spectrophotometer. Drug content is calculated as follows.[42]

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

**In-vitro release study**

The in vitro drug release studies are carried out using a modified Franz diffusion cell. The membrane is soaked in phosphate buffer pH 6.8 for 6 – 8 hr and is clamped carefully to one end of the hollow glass tube. Phosphate buffer of pH 6.8 is used as a diffusion medium. The emulgel sample is applied on the membrane and then fixed in between donor and receptor compartment of glass tube. The compartment of receptor contained phosphate buffer (100ml) of pH 6.8. The

temperature of the cell is thermostatically maintained at $37^0$C by circulating surrounding water in jacket and the solution is stirred continuously by magnetic stirrer at 500 rpm. The sample is withdrawn at suitable time intervals and is replaced by equal amounts of fresh diffusion medium. The samples are analyzed by using UV spectrophotometrically.[43]

**Skin irritation test**

The formulation of emulgel is applied topically on the properly shaven skin of rats and its adverse effects like change in morphology of skin such as change in colour should be checked up to 24 hours. The six numbers of rats (a set) is used for the study. If no irritation occurs then the test is passed. If the skin irritation symptoms occur in more than two rats the study should be repeated.[44]

**Stability studies**

The prepared emulgels are packed in aluminum collapsible tubes (15 gm) and subjected to stability studies at $5^0$C, $25^0$C/60%RH, $30^0$C/65% RH and $40^0$C/75% RH for a period of 3 months. Samples are withdrawn at each month as per ICH guidelines and analyzed for the physical appearance, pH, rheological properties, drug content, drug release profile etc.[45]

**Table 3: Current investigation of emulgel using different drugs**

| Drug | Aim | Use | Ref. |
|---|---|---|---|
| Ketoprofen | Biodegradable ingredient-based emulgel loaded with ketoprofen nanoparticles. | For the treatment of arthritis. | 46 |
| Ketoprofen | Technological and biopharmaceutical characterization of carbopol-based ketoprofen emulgels | Anti-inflammatory | 47 |
| Propolis | Propolis emulgel: a natural remedy for burn and wound | For and burn and wound treatment | 48 |
| **Oxiconazole** | Formulation of oxiconazole emulgel for topical drug delivery | **Fungal infection** | 49 |
| Itraconazole | Formulation, design and evaluation of microemulsion and micro-emulgel of itraconazole for topical application. | For the treatment of fungal infection | 50 |
| Itraconazole | Formulation and evaluation of topical itraconazole emulgel. | For the treatment of fungal infection | 51 |
| Ketoconazole | Formulation and evaluation of ketoconazole nanoemulgel. | For the treatment of fungal infection. | 52 |
| Terbinafine Hydrochloride | Formulation and evaluation of terbinafine hydrochloride film forming emulgel. | Antifungal activity | 53 |
| Amlodipine besylate | Formulation of amlodipine besylate emulgels for transdermal administration and its percutaneous permeability in vitro. | Transdermal delivery | 54 |
| Ketoconazole and acyclovir | Topical delivery of acyclovir and ketoconazole. | Viral and fungal cutaneous manifestations | 55 |
| Cyclosporin A | Formulation of Cyclosporin A emulgel for ocular delivery. | Topical ocular delivery | 56 |
| Diclofenac sodium | The evaluation of skin penetration of diclofenac from a novel topical non aqueous solution: A comparative bioavailability study. | Pain relief | 57 |
| Ketoprofen | Formulation of in vitro and in vivo evaluation of microemulsion-based gel loaded with ketoprofen. | Anti-inflammatory | 58 |
| Lacidipine | The novel non-ionic surfactant proniosomes for transdermal delivery of lacidipine: optimization using $2^3$ factorial design and in vivo evaluation in rabbits. | Antihypertensive | 59 |
| Metronidazole and ciprofloxacin | A groundnut oil based emulsion gels for passive and iontophoretic delivery of therapeutics. | Passive and iontophoretic delivery of therapeutics | 60 |
| Meloxicam | A formulation and characterisation of Meloxicam loaded emulgel for topical application. | Anti-inflammatory | 61 |
| Nimorazole | The preparation and evaluation of Radiosensitizing agent Nimorazole in topical emulgel. | Hypoxic cell radio sensitizing agent | 62 |

| | | | |
|---|---|---|---|
| Terpinen-4-ol | A effect of rheological behavior and microstructure of the emulgels on the release and permeation profiles of Terpinen-4-ol. | Anti-microbial property | 63 |
| Tioconazole | Formulation and Evaluation of Tioconazole Emulgel for Topical Drug Delivery System. | Antifungal | 64 |

**Table 4: Marketed Preparations**

| Drug | Product Name | Manufacturer |
|---|---|---|
| Miconazole nitrate, hydrocortisone | Miconaz-H-emulgel | Medical union pharmaceuticals |
| Azithromycine | Avindo gel | Cosmo pharma laboratories |
| Tezarotene | Zorotene gel | Elder pharmaceuticals |
| Diclofenac diethyl ammonium | Voltaren emulgel | Novartis pharma |
| Metronidazole | Lupigyl gel | Lupine pharma |
| Clindamycin phosphate, Allantion | Clinagel | Stiefel Pharma |
| Clobetasol propionate | Topinate gel | Systopic pharma |
| Aceclofenac, Methyl salisylate, Capsaicin | Acent gel | Intra Labs India Pvt. Ltd. |
| Benzoyl peroxide | Pernox gel | Cosme Remedies Ltd. |
| Clotrimazole,Beclomethasone, Dipropionate, Neomycin | Cloben gel | Indoco Remedies |
| Clindamycin, Adapalene | Excex gel | Zee Laboratories |
| Diclofenac diethyl amine | Diclobar emulgel | Barakat pharma |
| Diclofenac sodium | Pennsaid | Nuvo pharma |
| Hibiscus, liqourice and natural extracts | Levorag® emulgel | THD Ltd. |
| Kojic acid, Dipalmitate Arbuti, Octinoxate | Kojivit gel | Micro Gratia Pharma |

## CONCLUSION

Emulgels are novel drug delivery approach as they transport both hydrophobic and hydrophilic drug moiety by incorporating emulsion into gel phase. Amalgamation of emulsion into gel creates it a dual control release system and other problems such as phase partition, creaming related with emulsion get solved, and its consistency improves. Emulgel emerges better and advantageous medication delivery system as compare with other conventional topical treatment. They are suitable for almost all routes of delivery and consequently hold promise for different fields, be it cosmetics, curative or biotechnology. Due to its non-greasy, gel-like property it provides better release of drugs as compared to other topical drug delivery system. Drug delivered by emulgel can be proved harmless and effective and the pharma industries will profit considerably if clinical research can prove their potential intended for human use.

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