

Review Article

Emulgel: A novel drug delivery system

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Abstract Topical therapies in cream, ointment, gel and lotion formulation, are an important component of dermatological therapeutic armamentarium. They are relatively free of serious side effects. Emulgel, mixture of emulsion and gel, is relatively a new and novel topical drug delivery system which has many advantages and potential uses in dermatology. An O/W or W/O emulsion from selected oils on the basis of solubility with suitable emulsifier and a gel formulation is prepared. Then emulsion is incorporated into gel base and an optimized formula of emulgel with different grades and different concentration of gelling agent by applying suitable statistical design is obtained. Excipients are selected on the basis of solubility. Oil portion leads to improvement in penetration. All selected excipients could be selected to assist pharmacological action of antimicrobial agent.

Key words

Emulgel, emulsion, gel, topical preparation.

Introduction

Topical therapy has been used for centuries for the treatment of dermatological disorders. The spectrum of drugs/agents applied directly to the skin ranges from antiinflammatory, antiseptic, antibacterial, antifungal, antiviral, anti-acne, antipigmentary, anesthetic compounds to skin emollients and protectants. Topical route has the main advantage of direct delivery of drug to the target tissue i.e. skin and mucous membranes, bypassing the first-pass effect. However, skin permeation of a drug moiety from topical formulation is a multi-step process. It starts as release from the dosage form, diffusion through adhesive layer if it is present between the skin and drug loaded matrix, sorption or adhesion through stratum corneum, diffusion through stratum corneum, entry into the layer of the dermis (**Figure 1**).¹ Stratum corneum is barrier which prevents drug penetration.

Topical formulations can vary in consistency from solid, semisolid to liquid depending on their physicochemical properties. Besides the active substance (drug), each formulation has many non-medicinal ingredients (excipients) with diverse pharmacological functions. Sometimes more than one formulations can be combined to enhance the drug delivery. When a classical gel formulation is combined with an emulsion it is called EMULGEL.²

Emulsion

Emulsions are phases of two or more immiscible liquids. The one phase is dispersed into dispersed medium. Several types as oil in water (O/W), water in oil (W/O), oil in oil (O/O), micro-emulsions, double and multiple emulsions, mixed emulsions etc. for preparation and stability of emulsion the emulsifier is necessary.³ Various factors could affect the process of emulsification, such as the nature of oil, emulsifier, the emulsifier concentration used, rpm, as well as, the temperature.⁴

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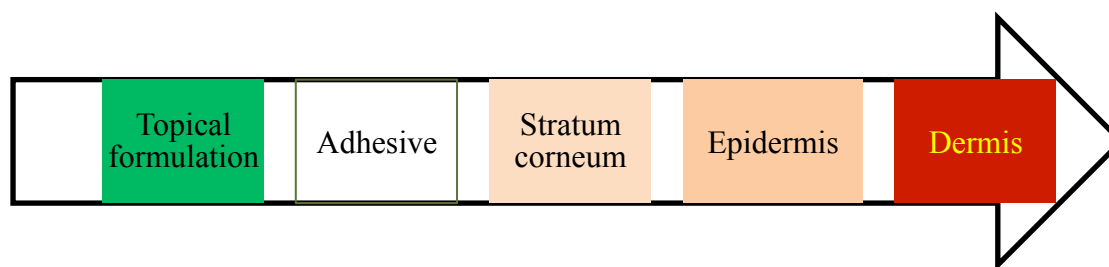


Figure 1 Path of drug penetration in topical dosage.

Table 1 Advantages of emulgels [2].

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

Gels

Gels are constituted by entrapment of large amounts of aqueous or hydroalcoholic liquid in a network of colloidal solid particles, which may be inorganic or organic polymers of natural or synthetic origin. The higher aqueous component permits greater dissolution of drugs, and permits easy migration of the drug as compared to the ointment or cream base. However, this makes gels poor vehicle for hydrophobic drugs. This limitation of gels can be overcome by making emulgel.²

Emulgel

Emulsion and gel could be mixed in preparation called emulgel,⁵ O/W emulsion for lipophilic materials while W/O for hydrophilic materials.⁶ Emulgels are thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, bio-friendly, transparent and cosmetically acceptable.² They also have good cutaneous penetration⁷ and long shelf-life.⁸ This all make emulgels an advantageous topical drug delivery system.

Rationale of emulgels as new formulation

Topical preparations like cream, ointment have many limitations like less spreading coefficient, less penetration through stratum corneum, less patient compliance due to stickiness or need to apply with rubbing etc. Similarly gels have the limitation of delivering hydrophobic drugs. Here emulgel could be prepared from selected oil on the term of solubility study of antimicrobial agent in them and emulsifier, so problem of solubility of drug can be almost overcome hence drug can be made available in solubilized form in emulgel, which can penetrate stratum corneum for drug action at viable soft tissue of skin. As globules of drug could penetrate stratum corneum comparatively larger surface area could be available for drug action, so less dose of drug may provide more pharmacological action.^{2,7,8} Moreover, selected other excipients may assist pharmacological action by one or other way. Emulgel could provide benefits of both emulsion and gel. Emulgel increases drug deposition over to the skin. However, emulsion has more bioavailability than emulgel but there is problem of stability and it has less patient compliance, as well. Topically used emulgel has various advantages over to ointment and gels (Table 1).

Requirements of chemical entities and excipients of an emulgel

Table 2 depicts the requirements and properties of chemical moieties of an emulgel. The relationship between log p value and skin permeability is not directly proportional, it decreases at both low and high end of

Table 2 Primary requirements of chemical moiety

Properties	Criteria
Effective concentration	less than 10 mg
$t_{1/2}$	≤ 10 hr.
Molecular mass	800 Dalton or less; desirably 500 Dalton or less; limit could indeed more than this by a change in permeability of skin.
log p value	0.8 to 5
Skin permeability coefficient	$\geq 0.5 \times 10^{-3}$ cm/hr.
Irritation to skin	Nonirritating
Polarity	Less
Molecular size	Small
pKa	Higher

Table 3 Ideal properties of excipient candidate

Properties	Criterion
Skin reaction	No-irritant and non-allergic
Effects on final preparation	Little or no deleterious effect on activity and stability
Regulatory status	IIG listed, GRAS listed or biologically safe
Concentration	Under regulatory limit
Compatibility	Compatible with API and the other excipients etc.

IIG: Inactive ingredients guideline; GRAS: Generally referred as safe; API: Active pharmaceutical ingredient

log p value, so log p value 5 is often taken as the highest limit. Oil to water partition coefficient of a substance gives idea about its lipophilicity and hydrophobicity.⁷ Excipients utilised should have ideal characteristics shown in **Table 3**.^{9,10,11}

Constituents [2,9,10]

Oils Mineral oil, different oils of vegetable origin (**Table 4**) or fish liver oil may be used.

Aqueous phase Rose water, sterile water

Emulsifier Tween-20, 40, 60, 80, PEG-300, 400, 600, Acrysol K-140, 150, 160, Glycerine, Span-20, 40, 60, Transcutol®-P, Sepineo™ SE 68.

Gelling agent Sepineo™ P 600, carbomer 934, 934P, 940, sodium alginate, HPMC, sodium CMC, Gellan gum.

Penetration enhancer Propylene glycol, clove oil, isopropyl myristate, olive oil, urea, DMSO, lauracapram, isopropyl palmitate, oleic acid, SLS, SDS, STGC, SDC, etc.

pH adjusting agent: NaOH, triethanolamine

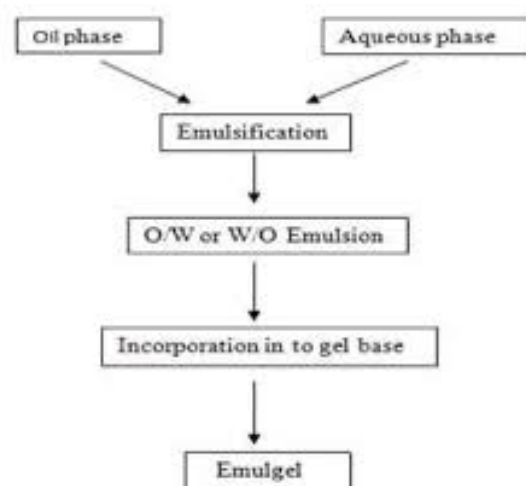


Figure 2 Basic steps in preparation of emulgel [2].

Preparation of emugel

There are three basic steps in the preparation of emulgel (**Figure 2**).²

Step 1 Formulation of emulsion either O/W or W/O.

Step 2 Formulation of gel base.

Step 3 Incorporation of emulsion into gel base with continuous stirring.

Table 4 Different oils which can be used for preparing emulgel.

<i>Oil</i>	<i>Unique property</i>
Black till oil	Antifungal
Coconut oil	Antifungal
Karanj oil	Antifungal
Neem oil	Antifungal
Jjoba oil	Antifungal, antibacterial
Eucalyptus oil	Penetration enhancer
Mentha oil	Antibacterial
Nutmeg oil	Antibacterial
Olive oil	Antibacterial
Chaulmoogra oil	Antibacterial

For standardization, emulgel can be evaluated by a number of methods.

Evaluation of emulsion

Viscosity Cone and plate rotational viscometer with spindle can be used to measure viscosity.

pH pH could be measured by digital pH meter.

Drug content Drug-loaded emulsion could be subjected to extract the drug from the emulsion in an appropriate solvent. Suitable dilution could be made with solvent and concentration could be measured by UV visible spectroscopic method at λ_{max} nm by keeping solvent as reagent blank.¹²

Centrifugation This parameter could be measured to evaluate physical stability. Emulsion could be centrifuged at ambient temperature and 5000 RPM for 10 minutes to evaluate the system for creaming or phase separation. System could be observed visually for appearance.¹³

Conductivity Electric conductivity of emulsion could be measured at ambient temperature with digital conductometer.

Dilution test If continuous phase is added into an emulsion, it could not be separated into phases. 50-100 times continuous phase dilution of emulsion could be carried out and visually checked for phase separation and clarity.¹⁴

Zeta potential and micelle size analysis

Micelle size, size distribution and zeta potential of emulsion could be determined using particle size analyzer.

Diffusion study By D-cell at 37°C using rate skin as a membrane.

Microbial assay of emulsion Ditch plate technique could be used for evaluation of bacteriostatic or fungistatic activity of an antimicrobial agent.

$$\% \text{ inhibition} = \frac{\text{length of inhibition}}{\text{whole length}} \times 100$$

optimization of emulsion using the suitable design of experiments, screening of gelling agent and its concentration, screening of penetration enhancer and its concentration if any, formulation of antimicrobial agent loaded emulgel.

Evaluation of emulgel

Physical Examinations Physical examination like Color, homogeneity, consistency, texture, etc.

pH 1% solution in water of emulgel subjected to measure pH by the digital pH meter.

Spreadability measurement 0.5 gm of emulgel is placed on a glass slide and a circle made around it. Then a second slide is placed over it and a predetermined weight is put on it for specific time period. The increase in diameter is noted as gm-cm/sec.¹⁵

Syneresis measurement test On rest gel shrinks and little liquid is pressed out called syneresis. This could be measured by means of centrifuge tubes in specific apparatus.¹⁶

$$\text{Syneresis (\%)} = \frac{\text{liquid separated from emulgel}}{\text{Total weight of emulgel before centrifugation}} \times 100$$

Rheological study Mainly viscosity can be determined at 37°C by the rheometer.

Drug content determination Drug content in emulgel could be estimated by the official method prescribed in pharmacopoeia.

Tube test (extrudability test) Determines force necessary for removal of emulgel from tube and necessary to evaluate emulgel formulation for extrudability.¹⁷

Diffusion study By D-cell at 37°C using rate skin.

Drug release kinetics study Data of diffusion study could be fitted in models of data treatment as zero, first, Higuchi model and various other models.¹⁸

Microbial assay of emulgel Ditch plate technique could be preferred for microbial assay and zone of inhibition calculated as per equation 1.

Optimization and development of emulgel by suitable statistical design of the experiment.

Skin irritation test of optimized batch of emulgel By Draize-patch test in the rabbit.

Microbial assay of optimized batch of emulgel by Ditch plate technique.

Accelerated stability study of optimized batch of emulgel Sample emulgel sealed in the ampoule and then put in equipment at specified temperature and relative humidity.⁷ Duplicate sample could be withdrawn at 1, 2, 3, 4, 5 and 6 month to evaluate their physicochemical parameters. The physical stability could be evaluated by visual inspection for physical changes. Chemical stability could be expressed as content of drug.^{19,20}

Comparison with available market preparation prepared optimized batch of

formulation could be compared with available market preparation of that antimicrobial agent by means of microbial assay study and if possible by means of animal study too.

Conclusion

Emulgel topical dosage form is a very useful addition to dermatological pharmacotherapy. If it would be possible to formulate emulgel of any drug moiety especially hydrophobic one, then it will increase drug efficacy, reduce its side effects and improve patients compliance.

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