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APPLICATIONS AND APPROACHES FOR EMULGELS

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ABSTRACT

Emulgel is a new approch of NDDS for topical drug transport. Emulgel has a double control release like emulsion and gel. Emulgel use for treating for muscle pain, headache, acne, psoriasis, rheumatoid arthritis. when emulsion and gel use in the combination its known as Emulgel. Emulgel is transparent gel which is used in pharmaceutical and cosmetic product. Emulgel overcome the problem which is come in gel and emulsion. Gel is new class of formulation, gel release drug faster in comparison of ointment, cream, lotion etc. Major limitation of gel is downside through transport of hydrophobic drug .so overcome this limitation Emulsion based approach use for delivery of drug to the skin. Different penetration enhancer use for better penetration. Emulgel is a better topical formulation in comparison of the conventional topical formulation.

KEYWORDS: Emulgels, topical, novel drug delivery.

INTRODUCTION

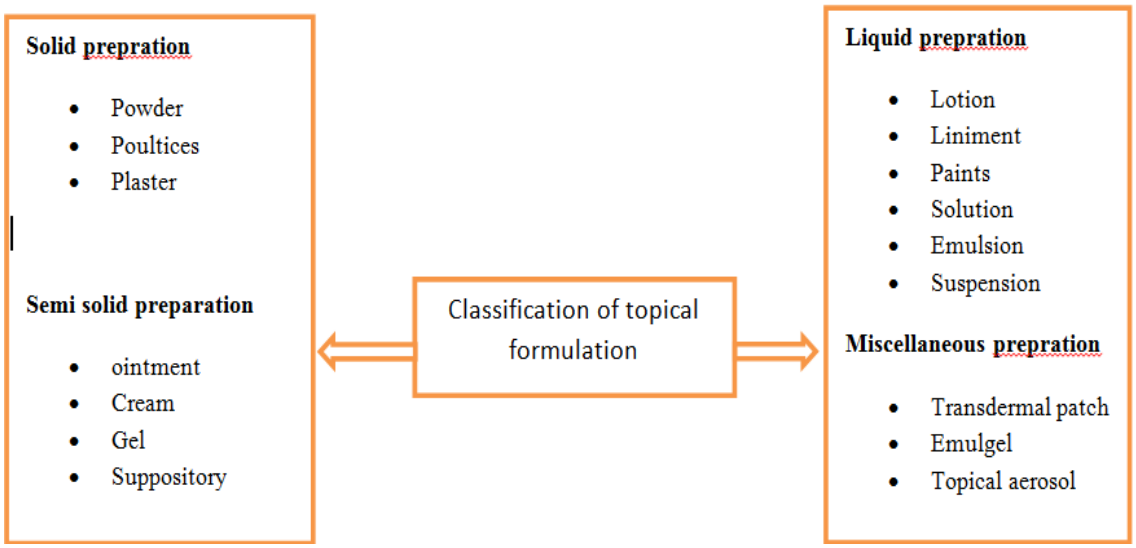
Topical drug delivery defines as delivery of drug through skin for treatment of topical infection and muscle pain, headache, arthritis. Topical drug delivery is a local drug delivery anywhere in the body through ophthalmic, nasal, rectal, vaginal and skin as topical routes. There are many advantages of topical drug delivery over the oral and parenteral route of drug delivery.[1]

The main advantage of topical drug delivery is

- Bypass of 1st pass metabolism
- Gastric irritation
- Unwanted enzymatic reaction
- **Avoid ADR**

Topical route of drug delivery use when another route of drug delivery doesn't provide an efficient result, or some drugs show incompatibility in git and ADR with GI fluid. Topical route are used for both cosmetic and dermatological. Different topical formulations are available in different form like solid, powder, semi-solid. Transparent emulgel having a many advantage like it can use in cosmetic and dermatological. gel is new class of formulation, which is transparent hydroalcoholic preparation, which have transparent, better loading capacity, better stability, better control release of drug, but the main disadvantage is hydrophobic moiety cannot delivery through skin easily. To overcome this problem we formulate the Emulgel. Emulsion based approach will facilitate to cross the drug moiety to permeate the skin.[2-4] Emulgel is a combination form of emulsion and gel. present of gelling base in water convert emulsion into Emulgel. O/w or W/O based Emulsion use for delivery of hydrophobic drug through the skin. Various natural polymer or synthetic polymer used as a gelling agent for the Emulgel. Emulgel has good stability, better control release, better loading capacity in comparison of gel, Emulsion, cream. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, water-soluble, longer shelf life, bio-friendly, transparent & pleasing appearance. Emulsions possess a certain degree of elegance and are easily washed off whenever desired.

Classification of topical formulation[4]



Factors Affecting Topical Absorption of Drug

Physiological Factors

- Skin thickness.
- Lipid content.
- Density of hair follicles.
- Density of sweat glands.
- Skin pH.
- Blood flow.
- Hydration of skin.
- Inflammation of skin

Physiochemical Factors

- Partition coefficient.
- Molecular weight (<400 dalton).
- Degree of ionization (only unionized drugs gets :<absorbed well).
- Effect of vehicles

Method to Enhance Drug Penetration and Absorption[5,6]

1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancemen

Advantages

1. Bypass first pass metabolism.
2. Avoidance of gastrointestinal incompatibility.
3. More selective to a specific site.
4. Better patient compliance.
5. Suitability for self-medication.
6. Providing utilization of drug with short biological half-life and narrow therapeutic window.
7. Ability to easily terminate medication when needed.
8. Comfortable and easy to apply.
9. Incorporation of hydrophobic drugs
10. Better loading capacity
11. Better stability

12. Production feasibility and low preparation cost
13. Controlled release
14. No intensive sonication

Disadvantages

1. Skin irritation on contact dermatitis.
2. The possibility of allergenic reactions.
3. The poor permeability of some drug through the skin.
4. Drug of large particle size not easy to absorb through the skin.
5. The occurrence of the bubble during formation of emulgel.

Physiology of skin[7-9]

For the topical preparation, it is necessary that the basic knowledge of the skin, its physiology function should be known for the designing of topical dosage form.

Average adult body skin having $2m^2$ surface area & one-third of the circulating blood received by skin. On every square of the human skin, contains approximately 40-70 hair follicles & 200-300 sweat ducts.

Non –viable epidermis

Actual physical barrier for the most of the substance is the stratum corneum which is the outermost layer of the skin.

Features of cell-flat

-plate-like structure

Size- 34-44 µm long

-25-36 µm wide

- 0.5-0.20 µm thick

Surface area – 750-1200 µm

Components- lipid (5-15%)

*Phospholipid

* Cholesterol sulphate

* Neutral lipid

-Protein (75-85 %)

Viable epidermis

This the layer which is lie between the stratum corneum & the dermis having thickness ranging from 50-100 µm. They are physiochemically similar to the other living tissues. Cells are engaged together by tonofibrils & water content is 90%.

Dermis

Just after the viable dermis, dermis is present. It consists a matrix of loose connective tissue and having thickness ranging from 2000-3000 µm. It is composed of a fibrous protein which is embedded in an amophorphose ground substance.

Subcutaneous connective tissue (SCT)

It is the innermost layer of the skin, which is also called as hypodermis. It is made up of fat % connective tissue and it is acts as an insulator & regulates body temperature.Cells which are exists between SCT are collagens, fat cels, nerve endings, hair follicle roots.[10]

Drug delivery through skin

The skin is the largest organ of the body, having total area of about 20 square feet. The skin performs various functions such as regulating body temperature, permits the sensations of touch, heat, and cold & protects from microbes.

Skin has three layers

- Waterproof barrier and creates our skin tone.
- The dermis, below the epidermis, contains tough connective tissue, hair follicles, and sweat glands.
- The deeper subcutaneous tissue (hypodermis) made from fat and connective tissue.

Penetration pathways

For topically applied drugs there are three penetrations pathways:[11,12]

- Intercellular
- Follicular
- Transcellular

Intercellular: drug transports through junction between the epithelial cells.

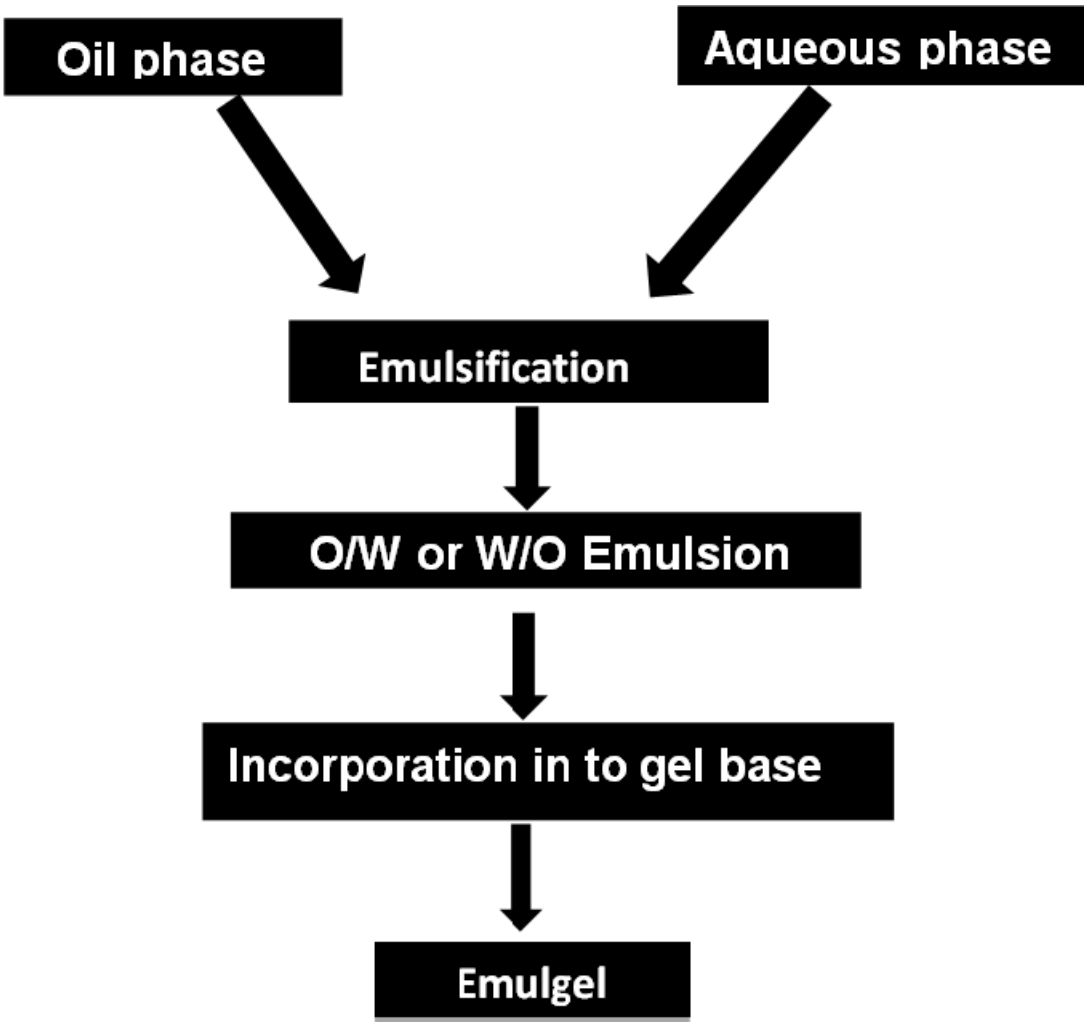
Intracellular: passage of drugs across the epithelial cells.

Follicular: for penetration of topically applied drugs hair follicles acts as a pathway.

Why emulgel?

There are a variety of topical preparation are available in market eg, Gel, emulsion, paste, creame, ointment, lotion etc. but these formulation have many disadvantage like low spreading coefficient, cause sticky, and also stability problem. To overcome these problem we use the emulgel. its a mixture of emulsion and gel. Emulsion is biphasic system that is employed for incorporation of hydrophobic medication through skin. Emulsion contain two-phase, oil phase and aqueous phase. Many hydrophobic drug cannot be incorporate in the semisolid preparation because of solubility is a main barrier. Gel is a newer class of formulation, where large amount of drug is incorporate. variety of semi solid formulation are used for topical treatment however emulgel overcome the problem related to conventional semisolid preparation. Emulgel show a much better bioavailability, stability, control release and spreadability.[13]

Flowchart of emulgel formulation[14]



METHOD OF PREPARATION

Step 1: Formulation of Emulsion (O/W or W/O)

Step 2: Formulation of gel base

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

Preparation of Emulgel was completed in 3 steps .in first step we prepare Emulsion either o/w or w/o. Emulsion were two phasic system that was essential to permeation of hydrophobic drug through skin. necessary ingredient are utilized in Emulsion is oil phase and liquid phase. Aqous phase was prepare by dissolve tween eighty in distill water and keep aside. the oil part was ready by the dissolving span eighty in liquid paraffin having the drug in ethanol solution. each the solution was heated individually at 70-80 °C. then water phase was add in oily part with continuous stirring till cooled at room temperature. Gelling base were ready by dissolve carbapol in H2O and dispersed HPMC in H2O for overnight. then the prepared emulsion was add in gelling base along non-stop stirred at gentle speed . ph of formulation was adjusted by the triethanolamine(TMA).[15-17]

Excipient used in emulgel preparation

Ideal property of excipient

1. Non toxic nature
2. Commercialy available
3. Must be compatible.
4. Must be physical and chemical stable with drug

Emulgel preparation component

Aqueous material

It's a aqous phase of emulsion. Commonly water and alcohol are used as a aqous phase for Emulgel.

Oils

These are use developing oil phase for Emulsion. There are differing kinds of oil phase that is employed within the Emugel formulation eg. mineral oil alone or paraffine combination, and non-biodegradable oil. Mineral oil are use commonly alone or with hard and light paraffin combination(according to drug and formulation). For eg, emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used each because the vehicle for the drug and for their occlusive and sensory characteristics. Wide used oils in oral preparations are

non-biodegradable mineral and castor oils that give a local laxative impact, and fish liver oils or numerous fixed oils of vegetable origin (e. g., Arachis, cottonseed, and maize oils) as nutritionary supplements. Oil extracted from totally different plants, contain medicative agents that is useful in local disease of the skin, wound healing, local injury, use in Emulgel formulation. There are variety of plant that contain these sort of medicative agents, like garlic oil, sesame oil, almond oil, jojoba oil, etc. jojoba oil contain antimicrobial, anti-inflammatory activity, we are able to use jojoba oil as a oil phase for any anti-inflamatory emulgel or antimicrobial emulgel. choice of jojoba oil as a oil phase it'll reduce the inflammation that is usually related to fungal infection.[18,19]

Table no 1:Eg. of oil.

Chemical	Quantity	formulation
Light Liquid Paraffin	7.5%	Emulgel
Propylene glycol	3-5%	Emulsion and Gel
Isopropyl stearate	7-7.5%	Emulsion
Isopropyl palmitate	7-7.5%	Emulsion

Emulsifiers

Emulsifying agents are used both to promote emulsification at the time of manufacture and to regulate stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations. There are different kind of emulsifying agent are employed in the preparation of emulsion. Emulsion are thermodynamically unstable or biphasic system, with use of emulsifying agent stability will increase. Emulsifying agents are selected by according to formulation and HLB value. Non-ionic surfactant that have greater HLB value than 8 (eg; spans, tween) are use within the formulation of o/w emulsion whereas mineral oil having HLB value less than eight are use in the formulation of w/o emulsion. mostly Emulgel formulation are prepare by the use of tween as a emulsifying agent in aqous phase and span twenty in its oily phase. But span, tweens as a emulsifying agent might cause the toxicity and stability problem thus overcome this problem we use biosurfactant. Biosurfactant are obtained from the microbs and having tiny fatty acid tail and polar head group.[20] They are attachéd to the hydrophilic or hydrophobic molecule. They have low toxicity, high biodigradablity and are environment friendly. These having higher stability, good foaming property at different temperature and different pH. The main purpose of emulsifying agent is reduce the interfacial surface tension between 2 immisible phase. Some of the emulsifying agents are below.

Table no 2: Eg. Of Emulsifiers[21]

Chemical	Formulation
polyethylene glycol 40 stearate	Emulgel and Emulsion
Sorbitan monooleate (span 80)	Emulgel and Emulsion
polyoxyethylene sorbitan monooleate (tween 80)	Emulgel and Emulsion
stearic acid	Emulsion
sodium stearate	Emulsion

Gelling agent

These are the agents used to increase the consistency of any dosage form also can be used as thickening agent. mainly these are two type natural and synthetic. the main purpose of using gelling agent, they make the formulation thixotropic. Carbapol and HPMC these area the 2 gelling agents that is often use for Emulgel. Carbapole is instantly absorb the water compared of HPMC. Carbapole and HPMC show a much better control release property. HPMC containing Emulgel show better control release.[22]

Table no 3: Eg. of gelling agent[23]

Gelling agent		Formulation
Synthetic	Natural	
Carbopol-934	Xanthan gum	Emulgel and Gel
Carbopol-940	Guar gum	Emulgel and Gel
HPMC-2910	Tragacanth	Emulgel and Gel
Sodium CMC		Gel

Permeation enhancers

These are a chemical or biochemical agent which interacts with skin constituents to induce a temporary increase in the skin permeability.

Properties of Penetration Enhancers[24]

They Should be non-toxic, nonirritant, and nonallergic.

They should have no pharmacological activity within body.

They should be cosmetically acceptable with an appropriate skin feel.

They should be appropriate for the formulation thus should be compatible with both excipients and drugs.

METHOD OF DRUG PERMEATION

1. Chemical Enhancement
2. Physical Enhancement
3. Biochemicalenhancement

4. Supersaturation Enhancement.

Table no 4: Eg of penetration enhancer.

Chemical	Formulation
Oleic acid	Emulgel and Gel
Lecithine	Emulgel and Gel
Urea	Emulgel and Gel
Isopropyl myristate	Emulgel and Gel
Linoleic acid	Emulgel and gel
Clove oil	Emulgel and Gel
Menthol	Emulgel and Gel
Cinnamon	Emulgel and gel

Evaluation of Emulgel[25-27]

1. Fourier transforms infrared spectroscopy (FTIR)

The primary aim of analysis of FTIR was to find a stable storage condition for the drug in solid state and excipient compatibility for Emulgel formulation.

2. Physical appearance

Each prepared Emulgel formulation is displayed for there physical representation like colour, grittiness homogeneity, consistency, Uniformity. Wether colour is white, pale yellow, off-white. Homogeneity and uniformity are examined by applying the Emulgel formulation on thin glass slide.

3. pH determination

pH meter is used for measuring the pH value of Emulgel formulation. Before use, ph meter should be caliberated with standard solution having ph 4-7. In distilled water 1gm of prepared Emulgel formulation was dissolved and stirred it to form a uniform suspension, kept it for 2hr. The volume made up to 100 ml and pH of the suspension can be measure with the digital pH meter.

4. Viscosity measurement

Brookfield Viscometer was used to determine viscosity of prepared Emulgel formulation. For the determination of viscosity, prepared Emulgel formulation was added to the beaker and setteled it for 30 mint at 25-30 °C. Adjust the spindal in that way that spindal does not touch the bottom of the jar and rotate at a moderate speed 40-70 RPM for 10 mint. The viscosity reading was noted.

5. Spreadability measurement

Two glass slide was used, which is same dimension used for determination of the prepared Emulgel formulation. Prepared Emulgel was placed over one slide and the other slide was placed over its top. The slide pressed upon each other like sandwich and remove the air bubble. Apply 2 gm of Emulgel is place between the slide and put 1 kg of weight on upper slide. Top plate was then subjected to pull of 80 grams. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5cm be noted. A shorter time to reach standard distance show a better Spreadability.[28]

6. Globule size and its distribution

Malvern zeta sizer is used for the determination of the globule size in prepared Emulgel formulation. Emulgel Formulation, whom globule size was determined, dissolved in distilled water and shakes it to get a uniform solution. Take well-defined amount of sample in photocell of zeta sizer. Mean globule size and its distribution in prepared Emulgel is collected.

7. Swelling index

Swelling index of prepared Emulgel was determined by the porous aluminum foil. Take 1-2gm of prepared Emulgel place it in 1N NaOH solution. Sample was taken from beaker at different time period and place it on dry place for some time re weight.[29]

Swelling index was calculated by following formula

Swelling Index (SW) % = [(Wt – Wo) / Wo] × 100

Where, (SW) %=equilibrium swelling percent

Wo= emulgel weight at zero time

Wt= weight of swollen Emulgel

8. Drug content determination

UV spectrometer was used for the determination of drug content of Emulgel formulation. Dissolve well-defined amount of Emulgel in suitable solvent with sonication. Absorption was determined by using proper dilution in UV spectrometer and Result were noted.

9. In vitro release study

Emulgel in vitro study was done on the Franz diffusion cell using egg membrane. Egg membrane clamped carefully at one end of glass tube of dylasis. A well-defined amount of Emulgel was applied on the egg membrane surface. The assembly has two chamber. Receptor

chamber and donor chamber. Receptor chamber is filled by the freshly prepared phosphate buffer having ph 7-8 for solubilizing the drug. Donar chamber use for sample withdrawing. Sample were collected different time interval and analyzed after suitable dilution in UV spectrometer. Cumulative % of drug release was calculated by the help of standard calibration curve.[30]

Drug content =(Conc.×D.F.×V.T.)×C.F.

D.F.= dilution factor

V.T.= Volume taken

C.F.= Conversion factor

10. Phase separation

Phase separation was done by using the centrifugation. All prepared Emulgel formulation were keep in centrifugation for 10 mint at 10,000 RPM and check if any phase separation obtained.

11. Skin irritation test

Skin irritation test of Emulgel was determined by using properly shaven skin of rat and rabbit. A group of 8 rat and rabbit can be used for the study. Weight accurately 1gm of Emulgel on the rat and rabbit skin and keep them in cage for next 24 hr. After 24 hr examine the rat and rabbit skin area, where the Emulgel formulation were applied check for any change occur in skin, colour change, any adverse effect noted. When no adverse effect were found formulation passed the test. If any adverse effect obtained in 2 or more then 2 rat then study should repeated.[31]

12. Extrudability

It is a typical observational test to quantify the power required to expel the material from tube. The technique connected for assurance of connected shear in the locale of the rheogram relating to a shear rate surpassing the yield esteem and showing resulting plug stream. In the present examination, the technique received for assessing Emulgel definition for extrudability depends on the amount in level of Emulgel and Emulgel expelled from lacquered aluminum collapsible tube on utilization of weight in grams required to expel no less than 0.5 cm lace of Emulgel in 10 seconds. More amount expelled better is extrudability. The estimation of extrudability of every detailing is in triplicate and the normal esteems are displayed. The extrudability is than ascertained by utilizing the accompanying recipe.

Extrudability =weight applied to extrude Emulgel from tube (in gm) / Area (in cm2).

Another technique to visualize the Extrudability of Emulgel formulation is applied using hardness tester. A fifteen weight unit of gel is stuffed in Al tube. The plunger was adjusted to carry the tube properly. The presence of one kg/cm was applied for thirty sec. the amount of gel extruded is weighed. The procedure is recurrent at three equidistance places of the tubes.[32]

13. Stability study

All Emulgel formulation were examined for the stability study. A well-defined amount (5gm) of Emulgel formulation was fill in alimunium tube place them for different temperature and RH enviourment. Temperature and RH is 5°C, 25°C/65%, 40°C/75% for next 3 months. Sample were taken at fifteen-day time interval and evaluate physical appearance, pH, rheological property, drug content, drug release profile.[33]

14. Drug release kinetic study

Drug release of topical formulation were calculated by the following equation.

(1) Zero order equation; Q=ko t

Q=amount of drug release

T=time

Ko=zero-order release constant

(2) 1^{ST} order equation; In(100-Q)=In 100-k1t

Q= % of drug release

T= time

K1= 1^{st} order release constant

(3) Higuchi equation; Q= k2√t

Q= % of drug release

T= time

K2= rate constant of diffusion

Emulgel formulation are used for following diseases

Acne

Acne is disorder of skin sebaceous gland and result in clogged pores and lesions commonly called pimples or jits. Prescription topical medications are erythromycin, clindamycin.[34,35]

Psoriasis

It is fundamentally an inflammatory skin condition with reactive abnormal epidermal differentiation and hyper proliferation affecting 2-3% of world population.[36] Topical treatments are usually the first to be tried when fighting psoriasis that includes emollients, dithranol, tar, deltanoids, corticoids, tacrolimus etc.

Atopic Dermatitis

It is a familial, chronic inflammatory skin disease that commonly presents during early infancy and childhood but can persist or start in adulthood. First line treatment includes Skin hydration and topical corticosteroids.[37]

Atopic Eczema

Atopic eczema is the commonest inflammatory skin disease of childhood. Itching, skin damage, redness, sores, sleep loss are various characteristics of eczema. Topical corticosteroids, topical calcinurin inhibitors, various emollients are used in its treatment.

Marketed formulation of Emulgel[38-40]

S.No.	Brand name	Active ingredient	Manufacturer	Use for
1	Voltarol 1.16% Emulgel	Diclofenac Diethylammonium	Novartis	Antiinflamatory
2	DiclomaxEmulgel	Diclofenac sodium	Torrent Pharma	Antiinflammatory
3	Miconaz-H-Emulgel	Miconazole nitrate, Hydrocortisone	Medical union Pharmaceuticals	Topical corticosteroid and antifungal
4	Dermafeet Emulgel	Urea 40%	Herbitas	Intense moisturizing and exfoliation activity
5	Isofen Emulgel	Ibuprofen	Beit jala pharmaceutical company	Anti-inflammatory
6	Diclona Emulgel	Diclofenac diethylamine	Kuwait Saudi pharmaceutical industries co.	Anti-inflammatory
7	Dosanac emulsion gel	Diclofenac diethylammonium	Siam bheasach	Anti-inflammatory
8	Diclon Emulgel	Diclofenac diethylamine	medpharma	Anti-inflammatory
9	Cataflam Emulgel	Diclofenac potassium	Novartis	Anti-inflammatory
10	Denacine Emulgel	Clindamycin phosphate	Beit jala pharmaceutical company	Antiacne

CONCLUSION

As the Emulgel is that the recent technique for the topical drug delivery it's higher appropriate for hydrophobic medication and obviously it's a really smart technique for drug delivery of combination of each hydrophilic and hydrophobic medication. Mainly the hydrophobic drug formulation may be developed using Emulgel technique as a result of it contain each oil and aqueous part whereas hydrogels aren't appropriate for hydrophobic medication. In future, topical drug delivery are used extensively to impart higher patient compliance. Since Emulgel is useful in enhancing Spreadability, adhesion, viscosity and extrusion, this novel drug delivery can become a popular formulation in future.

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