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A novel approach for topical delivery using emulgel

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Abstract
Many advantages of gels which are having a major limitation is the delivery of hydrophobic drugs. So, this limitation can be overcome by using an emulsion based approach where even a hydrophobic moiety can enjoy the unique property of gels. The combination of both gel and emulsion is referred as Emulgel. In recent years, there has been great interest in the use of novel polymers. A unique aspect of dermatological preparations is the direct accessibility of the skin as a target organ for the diagnosis and treatment. The combination of hydrophilic cornified cells in hydrophobic intercellular material provides a barrier for both hydrophilic as well as hydrophobic substances. Within the major group of semisolid preparations, the use of transparent gels has expanded both in pharmaceutical and cosmetic preparations. Polymer has a dual action which can function as emulsifier and thickeners because of gelling capacity of these compounds allows the formulation of stable emulsion and cream by decreasing the interfacial tension and surface area and at the mean while increasing the viscosity of the aqueous phase. In fact the gelling phase in the water phase converts the classical emulsion into emulgel. These emulgels are having major advantages on vesicular as well as on conventional systems in many aspects. Various penetration enhancers can potentiate the effect, hence emulgels can be used as better topical drug delivery systems over present drug delivery systems. The use of emulgel can be extended in analgesics and antifungal drugs.

Keywords: emulgel, hydrophobic drug, topical drug delivery

Introduction
Topical drug administration is a localized drug delivery system anywhere in the body such as ophthalmic vaginal, rectal and skin as topical routes. These are applicable for wide range such as for both cosmetics and dermatological preparations to the healthy or diseased skin [1]. Drugs are administered topically for their action at the site of application or for systemic effects [2]. Drug absorption through the skin is enhanced if the drug substance is present in the solution form, if it has a favourable lipid/water partition coefficient and if it is a non-electrolyte. For the most part, pharmaceutical preparations applied to the skin are intended to serve local action and as such are formulated to provide prolonged local contact with minimal systemic drug absorption. Drug applied to the skin for their local action include antiseptics, antifungal agent, skin emollient and protectant.
Advantages of topical drug delivery system: [3, 4]
1. To bypass first pass metabolism.
2. Avoidance of the risk and inconveniences of intravenous therapy and of the varied conditions of absorption like P^H changes, presence of enzymes, gastric emptying time.

The topical drug delivery system is generally used where the others system of drug administration fails or it is mainly used in fungal infection. Skin is the largest organ of the human body, providing around 10% of the body mass of an average person and it covers an average area of $1.7m^2$. Such a large and easily accessible organ apparently offers ideal and multiple sites to administer therapeutic agents for both local and systemic actions, human skin is a highly efficient self-repairing barrier designed to keep the inside in and outside out [5].
Gels are relatively newer class of dosage form created by entrapment of large amounts o aqueous or hydroalcoholic liquid in a network of colloidal solid particles which may consists of inorganic substance such as aluminum salts or organic polymers of natural or synthetic origin [6]. They have a higher aqueous component that permits greater dissolution of drugs, and also permit easy migration of the drug through a vehicle that is essentially a liquid, compared with the ointment or cream base [7]. These are superior in terms of use and patient acceptability. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs.

So to overcome this limitation, emulgels are prepared and used so that even a hydrophobic therapeutic moiety can enjoy the unique properties of gels [8-11].

In fact, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel [12]. Both oil-in water and water-in-oil emulsions are used as vehicles to deliver various drugs to the skin. Emulgels for dermatological use have several favorable properties such as being thixotropic, greaseless, easily spreadable, easily removable, emollient, non-staining, long shelf life, bio-friendly, transparent & pleasing appearance.

Use of topical agents requires an appreciation of the factors that influence percutaneous absorption.14 Molecules can penetrate the skin by three routes: through intact stratum corneum, through sweat ducts, or through sebaceous follicle. The surface of the stratum corneum presents more than 99% of the total skin surface available for percutaneous drug absorption [15].

Passage through this outer most layer is the ratelimiting step for percutaneous absorption. The major steps involved in percutaneous absorption include the establishment of a concentration gradient, which provides the driving force for drug movement across the skin, release of drug from the vehicle (partition coefficient), and drug diffusion across the layers of the skin (diffusion coefficient). Preferable characteristics of topical drugs include low molecular mass (600 Da), adequate solubility in oil and water, and a high partition coefficient. Except for very small particles, water soluble ions and polar molecules do not penetrate intact stratum corneum. Topical formulation can be used to manipulate the barrier function of the skin, for example, topical antibiotics and antibacterials help a damaged barrier toward off infection, sun screening agents and the horny layer protect the viable tissues from Ultraviolet radiation and emollient preparations restore pliability to a desiccated horny layer [16].

During development of semi-solid preparations for cutaneous application whose formulation contains an antimicrobial preservative, the need for and the efficacy of the chosen preservative shall be demonstrated to the satisfaction of the competent authority. A suitable test method together with criteria for judging the preservative properties of the formulation are provided in efficacy of antimicrobial preservation. Sterile semi-solid preparations for cutaneous application are prepared using materials and methods designed to ensure sterility and to avoid the introduction of contaminants and the growth of microorganisms [17].

The efficacy of an antimicrobial preservative may be enhanced or diminished by the active constituent of the preparation or by the formulation in which it is incorporated or by the container and closure used. Preparation for topical use should have mircobiologial quality and it is checked with test for sterility. Total viable aerobic count should not be more than 102 micro-organisms (aerobic bacteria plus fungi) per gram. It should not have more than 101 enterobacteria, certain other gram-negative bacteria per gram and completely devoid of Pseudomonas aeruginosa and Staphylococcus aureus [18, 19].

This project is to reveal the material and method used does'nt imparts any microbial contamination and the methyl paraben 0.2% used is sufficient to maintain its sterility. (Micro biology)

Rationale

Many widely used topical agents like ointment, cream, lotion have many disadvantages. They have very sticky causing uneasiness to the patient when applied. Moreover they also have lesser spreading coefficient and need to apply with rubbing. And they exhibit the problem of stability also. Due to all these factors within the major group of semisolid preparations, the use of transparent gels has expanded both in cosmetics and in pharmaceutical preparations.

A gel is colloid that is typically 99% wt liquid, which is immobilized by surface tension between it and a macromolecular network of fibers built from a small amount of a gelating substance present. In spite of many advantages of gels a major limitation is in the delivery of hydrophobic drugs. So to overcome this limitation an emulsion based approach is being used so that even a hydrophobic therapeutic moiety can be successfully incorporated and delivered through gels [20].

Drug delivery across the skin

The epidermis is the most superficial layer of the skin and is composed of stratified keratinised squamous epithelium which varies in thickness in different parts of the body. It is thickest on with elastic fibres. The skin forms a relatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important is a continuous venous plexus that is supplied by inflow of blood from the skin capillaries. In the most exposed areas of the body-the hands, feet, and ears blood is also supplied to the plexus directly from the small arteries through highly muscular arteriovenous anastomoses. A unique aspect of dermatological pharmacology is the direct accessibility of the skin as a target organ for diagnosis and treatment. The skin acts as a two-way barrier to prevent absorption or loss of water and electrolytes. There are three primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs pass through the torturous path around corneocytes and through the lipidbilayer to viable layers of the skin. The next most common (and potentially under recognized in the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides in the outermost layer of the epidermis, the stratum corneum, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum corneum or whole skin. Creams and gels that are rubbed into the skin have been used for years to deliver pain medication and infection fighting drugs to an affected site of the body. These include, among others, gels and creams for vaginal yeast infections, topical creams for skin infections and creams to soothe arthritis pain. New technologies now allow other drugs to be absorbed through the skin (Transdermal). These can be used to treat not just the affected areas (for example, the skin) but the whole body. (Systemic).

Factors Affecting Topical Absorption of Drug [21, 22]

Physiological Factors

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.
8. Inflammation of skin

Physiochemical Factors
1. Partition coefficient.
2. Molecular weight (<400 daltons)
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.

Factors to be Considered When choosing a Topical Preparation [23, 24]
1. Effect of the vehicle e.g. An occlusive vehicle enhances penetration of the active ingredient and improves efficacy. The vehicle itself may have a cooling, drying, emollient or protective action.
2. Match the type of preparation with the type of lesions. For example, avoid greasy ointments for acute weepy dermatitis.
3. Match the type of preparation with the site.(e.g., gel or lotion for hairy areas)
4. Irritation or sensitization potential. Generally, ointments and w/o creams are less irritating, while gels are irritating. Ointments do not contain preservatives or emulsifiers if allergy to these agents is a concern.

Method to enhance drug penetration and absorption [25]
1. Chemical enhancement
2. Physical enhancement
3. Biochemical enhancement
4. Supersaturation enhancement.

Advantages [26, 27]: Hydrophobic drugs can be easily incorporated into gels using d/o/w emulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility act as a barrier and problem arises during the release of the drug. Emulgel helps in the incorporation of hydrophobic drugs into the oil phase and then oily globules are dispersed in aqueous phase resulting in o/w emulsion. And this emulsion can be mixed into gel base. This may be proving better stability and release of drug than simply incorporating drugs into gel base.
1. Better stability: Other transdermal preparations are comparatively less stable than emulgels. Like powders are hygroscopic, creams shows phase inversion or breaking and ointment shows rancidity due to oily base.
2. Better loading capacity: Other novel approaches like niosomes and liposomes are of nano size and due to vesicular structures may result in leakage and result in lesser entrapment efficiency. But gels due to vast network have comparatively better loading capacity.
3. Production feasibility and low preparation cost: Preparation of emulgels comprises of simpler and short steps which increases the feasibility of the production. There are no specialized instruments needed for the production of emulgels. Moreover materials used are easily available and cheaper. Hence, decreases the production cost of emulgels.
4. No intensive sonication: Production of vesicular molecules need intensive sonication which may result in drug degradation and leakage. But this problem is not seen during the production of emulgels as no sonication is needed.
5. Controlled release: Emulgels can be used to prolong the effect of drugs having shorter t1/2.

Formulation of Emulgel

1. Aqueous Material

This forms the aqueous phase of the emulsion. Commonly used agents are water, alcohols [28].

2. Oils

These agents form are given in table 1, the oily phase if the emulsion. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffins, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics. Widely used oils in oral preparations 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, cottonseed, and maize oils) as nutritional supplements [29, 30].

3. Emulsifiers

Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Polyethylene glycol 40 [31] stearate, Sorbitan monooleate [32] (Span 80), Polyoxyethylene sorbitan monooleate (Tween 80) [33], Stearic acid [34], Sodium stearate [35].

4. Gelling Agent: [36, 37]

These are the agents used to increase the consistency of any dosage form can also be used as thickening agent. given in table 2

5. Permeation Enhancers

These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability [38].

Emulgel Preparation

Emulgel was prepared by the method reported by Mohammad *et al*. (2004) with minor modification. The Gel in formulations were prepared by dispersing Carbopol 934 in purified water with constant stirring at a moderate speed and Carbopol 940 in purified water with constant stirring at a moderate speed then the pH are adjusted to 6 to 6.5 using Tri ethanol amine (TEA).

The oil phase of the emulsion were prepared by dissolving Span 20 in light liquid paraffin while the aqueous phase was prepared by dissolving Tween 20 in purified water. Methyl and Propyl paraben was dissolved in propylene glycol whereas drug was dissolved in ethanol and both solutions was mixed with the aqueous phase. Both the oily and aqueous phases were separately heated to 70° to 80°C; then the oily phase were added to the aqueous phase with continuous stirring until cooled to room temperature. And add Glutaraldehyde in during of mixing of gel and emulsion in ratio 1:1 to obtain the emulgel [39].

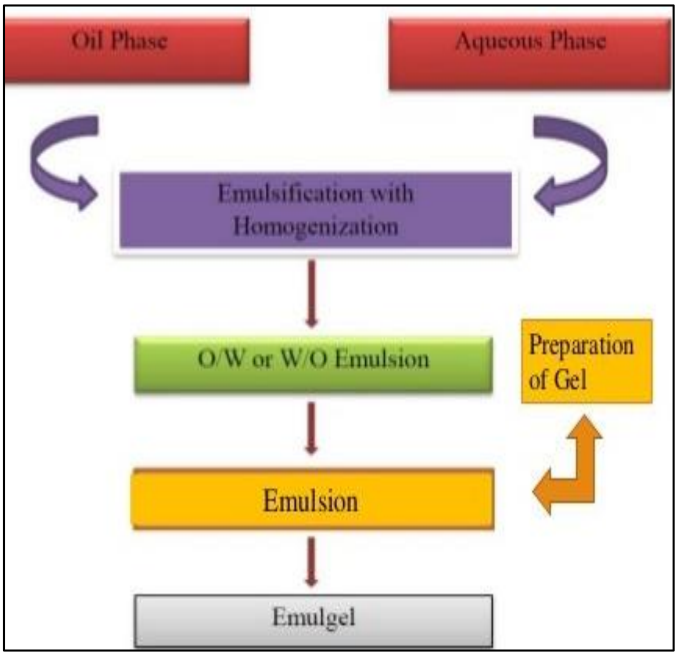

Fig 1: Flow chart of emulgel formulation

Characterization of Gellified Emulsion

1. Physical appearance: The prepared Emulsion formulations were inspected visually for their color, homogeneity, consistency and pH. The pH values of 1% aqueous solutions of the prepared Gellified Emulsion were measured by a pH meter (Digital pH meter DPH 115 pm) [40].

2. Spreadability: Spreadability is determined by apparatus suggested by Mutimer *et al*. (1956) which is suitably modified in the laboratory and used for the study. It consists of a wooden block, which is provided by a pulley at one end. By this method, spreadability is measured on the basis of 'Slip' and 'Drag' characteristics of emulgels. A ground glass slide is fixed on this block. An excess of emulgel (about 2 gm) under study is placed on this ground slide [41]. The emulgel is then sandwiched between this slide and another glass slide having the dimension of fixed ground slide and provided with the hook. A 1 Kg weight is placed on the top of the two slides for 5 minutes to expel air and to provide a uniform film of the emulgel between the slides. Excess of the emulgel is scrapped off from the edges. The top plate is then subjected to pull of 80gms. With the help of string attached to the hook and the time (in seconds) required by the top slide to cover a distance of 7.5 cm be noted. A shorter interval indicate better spreadability. Spreadability was calculated by using the formula.

$$S = M.L/T$$

Where
S = spreadability,
M = Weight tied to upper slide,
L = Length of glass slides
T = Time taken to separate the slides completely from each other.

3. Extrudability study: It is a usual empirical test to measure the force required to extrude the material from tube. The method applied for determination of applied shear in the region of the rheogram corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow. In the present study, the method adopted for evaluating emulgel formulation for extrudability is based upon the quantity in percentage of emulgel and emulgel extruded from lacquered aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds [42]. More quantity extruded better is extrudability. The measurement of extrudability of each formulation is in triplicate and the average values are presented. The extrudability is than calculated by using the following formula:

Extrudability = Applied weight to extrude emulgel from tube (in gm) / Area (in cm2)

Globule size and its distribution in emulgel: Globule size and distribution was determined by Malvern zetasizer. A 1.0 gm sample was dissolved in purified water and agitated to get homogeneous dispersion. Sample was injected to photocell of zetasizer. Mean globule diameter and distribution was obtained [43].

Rheological Study: The viscosity of the different emulgel formulations is determined at 25°C using a cone and plate viscometer with spindle 52 (Brookfield Engineering Laboratories,) and connected to a thermostatically controlled circulating water bath.

4. Swelling Index: To determine the swelling index of prepared topical emulgel, 1 gm of gel is taken on porous aluminum foil and then placed separately in a 50 ml beaker containing 10 ml 0.1 N NaOH [44]. Then samples were removed from beakers at different time intervals and put it on dry place for some time after it reweighed.

Swelling index is calculated as follows:

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

Where,
(SW) % = Equilibrium percent swelling,
Wo = Original weight of emulgel at zero time after time t,
Wt = Weight of swollen emulgel

Ex–vivo Bioadhesive strength measurement of topical emulgel:

(MICE SHAVEN SKIN): The modified method is used for the measurement of bio adhesive strength. The fresh skin is cut into pieces and washed with 0.1 N 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 right and left 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 [45]. 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 bio adhesive strength. The bio adhesive strength is calculated by using following:

$$\text{Bioadhesive Strength} = \text{Weight required (in gms)} / \text{Area } (cm^2)$$

5. Drug Content Determination: Drug concentration in Gellified Emulsion was measured by spectrophotometer. Drug content in Gellified Emulsion was measured by dissolving known quantity of Gellified Emulsion in solvent (methanol) by Sonication. Absorbance was measured after suitable dilution in UV/VIS spectrophotometer (UV-1700 CE, Shimadzu Corporation, Japan) [46].

6. *In Vitro* Release Study: Franz diffusion cell (with effective diffusion area 3.14 cm2 and 15.5 ml cell volume) was used for the drug release studies. Gellified Emulsion (200 mg) was applied onto the surface of egg membrane evenly. The egg membrane was clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber was filled with freshly prepared PBS (pH 5.5) solution to solubilize the drug. The receptor chamber was stirred by magnetic stirrer. The samples (1.0 ml aliquots) were collected at suitable time interval. Samples were analyzed for drug content by UV visible spectrophotometer after appropriate dilutions. Cumulative corrections were made to obtain the total amount of drug release at each time interval. The cumulative amount of drug released across the egg membrane was determined as a function of time.

7. Microbiological assay: Ditch plate technique was used. It is a technique used for evaluation of bacteriostatic or fungistatic activity of a compound. It is mainly applied for semisolid formulations. Previously prepared Sabouraud's agar dried plates were used. Three grams of the Gellified Emulsion are placed in a ditch cut in the plate. Freshly prepared culture loops are streaked across the agar at a right angle from the ditch to the edge of the plate. After incubation for 18 to 24 hours at 25°C, the fungal growth was observed and the percentage inhibition was measured as follows.

% inhibition = L2 / L1 × 100

Where L1 = total length of the streaked culture,
L2 =length of inhibition.

8. Skin irritation test: A 0.5 gm sample of the test article was then applied to each site (two sites per rabbit) by introduction under a double gauze layer to an area of skin approximately 1" x 1" (2.54 x 2.54 cm2). The Gellified Emulsion are applied on the skin of rabbit. Animals were returned to their cages. After a 24 hour exposure, the Gellified Emulsion are removed. The test sites were wiped with tap water to remove any remaining test article residue.
Accelerated stability studies of Gellified Emulsion: Stability studies were performed according to ICH guidelines. The formulations were stored in hot air oven at 37 ± 2°, 45 ± 2° and 60 ± 2° for a period of 3 months. The samples were analyzed for drug content every two weeks by UV-Visible spectrophotometer. Stability study was carried out by measuring the change in pH of gel at regular interval of time.

Table 1: Use of oil

Chemical	Quantity (%)	Dosage form
Light liquid paraffin	7.5	emulsion and emulgel
Isopropyl myristate	7–7.5	emulsion
Isopropyl stearate	7-7.5	emulsion
Isopropyl palmitate	7-7.5	emulsion
Propylene glycol	3-5	Gel

Table 2: Use of gelling agents

Gelling agent	Quantity (%)	Dosage form
Carbopol-934	1	Emulgel
Carbopol-940	1	emulgel
HPMC-2910	2.5	Emulgel
HPMC	3.5	Gel
Sodium CMC	1	Gel

Table 3: Marketed preparations

Product	Drug	Manufacture
Voltaren emulgel	Diclofenac-diethyl-ammonium	Novartis pharma
Miconaz-H-Emulgel	Miconazole nitrate, hydrocortisone	Medical union pharmaceuticals
Excel gel	Clindamycin, adapalene	Zee laboratories
Pernox gel	Benzoyl peroxide	Cosme remedies Ltd
Lupigyl gel	Metronidazole, clindamycin	Lupin pharma
Clinagel	Clindamycin phosphate, allantonin	Stiefel pharma
Topinate gel	Clobetasol propionate	Systopic pharma
Kojivit gel	Kojic acid, dipalmitate acid	Micro gratia pharma
Accent gel	Aceclofenac	Intra labs India Pvt. Ltd
Avindo gel	Azithromycin	Cosme pharma lab
Cloben gel	Clotrimazole, betamethasone	Indoco remedies
Nadicin cream	Nadifloxacin	Psycho remedies
Zorotene	Tazarotene	Elder pharmaceuticals

Marketed Preparations

The various preparations of emulgels available in market are shown in table 3

Future prospective

Table 4: Current study and development on emulgel formulation.

Study	Drug	Polymer	Enchancer	Purpose	References
Formulation, development and *in vitro* evaluation	Terbinafine hydrochloride	Carbopol 934	Propylene glycol	Fungal infection	[47, 48]
Preparation, characterization and pharmacodynamic evaluation	ketoprofen	HPMC	Propylene glycol	Anti-inflammatory	[49]
Formulation and evaluation	Mefenamic acid	Carbopol 934	Propylene glycol	Anti-inflammatory	[50]
Formulation and optimization	chlorophenesin	Carbopol 934	Propylene glycol	Antifungal	[51]
Formulation, design and development	Piroxicam	Carbopol 934	Propylene glycol	Anti-inflammatory	[52]
Development and optimization	Diclofenac	HPMC	Propylene glycol	Anti-inflammatory	[47, 53]
Formulation and evaluation	Commiphora mukul+Psoralea corylifolia	Carbopol 934	Propylene glycol	Antipsoriatic	[54]
Preparation and evaluation	clotrimazole	Carbopol 934	Propylene glycol	Antifungal	[47, 55]
Development and characterization	Clarithromycin	Carbopol 934	Propylene glycol	Broad spectrum	[56]

				antibiotic	
Development and chacterization	ketoconazole	HPMC	Propylene glycol	Antifungal	[47, 57]
Formulation and *in vitro* evaluation	Ciprofloxacin	Carbopol 934	Propylene glycol	antimicrobial	[47, 58]
optimization	chlorphenism	Carbopol 934, HPMC	Propylene glycol	Effect of gelling agent	[58]
Development and characterization	ketoconazole	Carbopol 934,940	Propylene glycol	Comparative study of polymer and drug release	[59]
Percutaneous absorption study	Diclofenac	carbopol 934, 940, HPMC	Transcutol, myrj 52 cineol	Effect of penetration enhancer	[47,59]
Development study	Miconazole	Carbopol 934, 940	Propylene glycol	Controlled delivery, antifungal	[60]
Formulation	Itraconazole	Carbopol 934,940	Propylene glycol	More selective, antifungal	[61]
Formulation, design, development, evaluation	Meloxicam	Carbopol 934	DSMO, menthol, clove oil, oleic acid	Treatment of rheumatoid arthritis	[62]
Formulation, evaluation	Capsicum frutescens L	Carbomer	Menthol, propylene glycol	Analgesic	[63]
Formulation, evaluation	guggulsterone	Xanthum gum	Propylene glycol	Anti-arthritic	[64]
Formulation, evaluation	Lantana camara	Carbopol 934, HPMC K15M,HPMC	Propylene glycol	Wound healing activity	[65]
Formulation, development, evaluation	Indomethacin	HPMC K4M, xanthum gum,	Propylene glycol	Used for four types of gelling agent	[66]
Formulation, evaluation of nano emulgel	adapalene	Carbopol 934	Soyabean oil	Decreases systemic side effect	[67]
Formulation, evaluation	Loratadine	Carbopol 934	Propylene glycol	Treatment of localized skin allergy	[68]
Formulation, evaluation	Itraconazole	Carbopol 934, 940	Propylene glycol	Antifungal	[69]
Formulation, charcterization	ketoprofen	Carbopol 934,HPMC K4M, K15M	Propylene glycol	Anti-inflammatory	[70]
Formulation, evaluation	Indomethacin	Carbopol 934, xanthum gum	Propylene glycol	Using two types of polymers	[71]

Conclusion

In the coming years, topical drug delivery will be used extensively to impart better patient compliance. Since emulgel possesses an edge in terms of spreadibilty, adhesion, viscosity and extrusion, they will become a popular drug delivery system. Moreover, they will become a solution for loading hydrophobic drugs in an water soluble gel bases.

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