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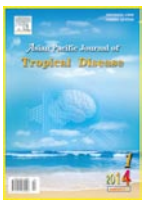

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Micro-emulsion based emulgel: a novel topical drug delivery system

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PEER REVIEW

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Comments

This is a good review article in which author try to provide topical formulation having advantages of both micro-emulsion and emulgel providing high biavailibility of drug. The drug loaded micro-emulsion based emulgel drug delivery system can be an effective novel topical formulation for the fast relief from chronic condition. The micro-emulsion based emulgel gives two to four folds more efficacy than marketed topical product, so that less dose and dose frequency is required.
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ABSTRACT

Topical delivery systems for drugs make localized administration of the drug anywhere in the body through ophthalmic, vaginal, skin and rectal routes. Topical formulations encompass a wide variety of formulations intended for cosmetic or dermatological application, to healthy as well as diseased skin. Drugs may be administered for localized or systemic effect. Topical preparations can be formulated with varying physico-chemical properties, as solid, semisolid or liquid. Micro-emulsion of drug is prepared and incorporated into emulgel, having novel topical drug delivery system as dual release control system. Micro-emulsions are micronized; thermodynamically stable systems having low interfacial tension prepared by adding co-surfactant have several features like enhanced permeability, good thermodynemic stability and prolong release. Emulgel prolongs the drug release, increases patient compliance and stability of emulsion. The prepared emulgel is evaluated for various parameteres like pH, viscosity, globule size; spreadability *etc*. whereas micro-emulsion is evaluated for various parameters like viscosity, pH, zeta-potential *etc*.

KEYWORDS

Microemulgel, Micro-emulsion, Emulgel, Topical drug delivery system

1. Introduction

In last few years the treatment of illness has been accomplished by administering drug to human body via various routes, namely, oral, sublingual, rectal, parental *etc*. The topical drug delivery system is generally used in where other systems of drug administration fails or it is mainly used in local skin infection like fungal infection. Topical drug delivery can be defined as the application of a drug containing formulation to the skin to directly treat cutaneous disorder[1,2].

Nowadays scenario pharmaceutical research work is focused to fulfil the therapeutic needs of patients. Most of active pharmaceutical ingredients developed are

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hydrophobic in nature, so to develop new drug delivery system micro-emulsion has good impact on effective delivery of hydrophobic drugs[3,4].

Most of widely used drugs when given by oral route have side effects like gastric irritation, nausea, bleeding in gastrointestinal tract *etc*. In order to minimize such side effects and systematic toxicities and also achieve better therapeutic effects one of the promising method is to administered drug via skin or, inshort, topical drug delivery system.

The transdermal drug delivery systems provide very important tools to get these benefits and also control or sustain the active moities and increases patient acceptance[5].

Topical applications of several moities widely used in several diseases treatments is a substitute route to overcome the adverse effects of oral and rectal route of administration[6]. The concept of micro-emulsions was first introduced by Hoar and Schulman during 1940s[7]. It is defined as a system of water, oil and amphiphile which is an optically isotropic and thermodynamically stable liquid micro-dispersion. Micro-emulsion is the vehicle for improving the delivery, efficacy and bioavailibility of several drugs. Micro-emulsions are themodynamically stable transparent, isotropic, low viscosity colloidal dispersions containing oil and water stabilized by an interfacial film consisting of surfactan/co-surfactant. Micro-emulsions have several advantages like thermodynamic stability, ability to be entraped hydrophilic, hydrophobic therapeutic agents *etc*. enhencing dermal transport of chemical moities due to lipophilicity and improving permeabilities due to presence of surfactants. While in the manufacturing point of view micro-emulsions involves comparatively very less numbers of unit operations in the formulation and development which is cost effective, less time consuming and convenient as well. Moerever micro-emulsion has change in thermo-dynamic activity of drugs they contain, modifying their partition co-effiecient. Thus it has more penetration through stratum corneum, and its ingredients, surfactants and co-surfactants, reduces the functional barrier of the stratum corneum.

While microemulgel, the combined form of micro-emulsion and gel have advantage of both micro-emulsion and gel[8,9]. Emulgels for dermalogical use have several advantages like thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent and pleasing appearance[10].

2. Anatomy and physiology of skin

The skin of average adult body covers surface area approximately 2 m^2 and receive about one third of blood circulating through body. An average human skin surface is mainly contains forty to seventy hair follicles and two to three houndreads of sweat ducts per square meter of skin. The pH of skin varries from 4 to 5.6. Sweat and fatty acid secreted from sebum influence the pH of skin. The skin consists of four distinct layers of tissues, namely, non-viable epidermis, viable epidermis, viable dermis and subcutaneous connective tissues (Figure 1)[11-13].

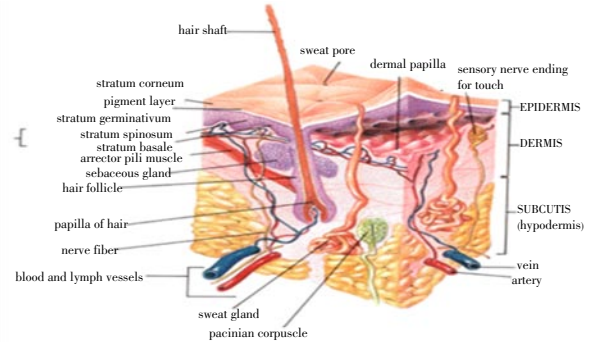

Figure 1. Anatomy of skin[13].

3. Topical drug delivery system

There are two basic types of topical drug delivery products, external topicals and internal topicals. The external topicals are spread, sprayed or otherwise dispersed on the tissue to cover diseased area, whicle the internal topicals are applied to mucous membrane orally, vaginally or on the rectal tissues for local activity. Main advantages of topical drug delivery system are avoiding first pass metabolism, avoiding gastrointestinal incompatibilities, specific site selective, improving patients compliance, possible and eassy self-medication, and drugs with short half-life and narrow therapeutic index are also subjected to be utilised, facility is used to eassily terminate medicines whenever required[14].

Disadvantages of topical drug delivery sytem are skin irritation on contact dermatitis, possibilities of allergic reactions, poor permeability of drugs through skin, drugs of large particle size are not absorbed eassily through skin. Skin is thick, complex in structure. Molecules moving from the environment must penetrate the stratum corneum and any material of endogenous or exogenous origin on its surface. They must then penetrate the viable epidermis, the papillary dermis and the capillary walls into the blood stream or lymph channels, whereupon they are removed from the skin by flow of blood or lymph. To move across the skin membrane is obviously a complex phenomenon and challenge in analysis. Factors influencing the topical drug delivery system can be physiological factors *e.g*. thickness, hydration, imflammation and pH of skin, lipid content, densities of hair follicles and sweat glands, blood flow *etc*., and physico-chemical factors like partition co-efficient, molecular weight, degree of ionization, effect of vehicle *etc*[15].

When moity reaches intact skin, it contacts cellular debris, microorganisms, sebum and the othe materials. The diffusion of drug will be done by various routes via hair follicles, sebaceous gland and sweat ducts across the contineous stratum corneum (Figure 2).

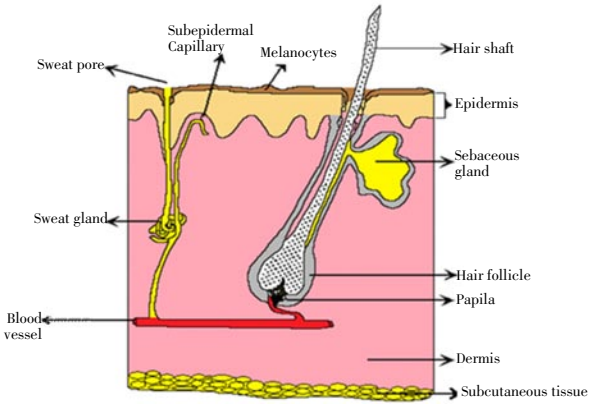

Figure 2. Various routes of penetration of drugs throgh skin[16].

Various factors like effect of vehicle matching of type of preparations with type of lessions *etc.* are considered while choosing topical preparations[17,18].

4. Rational

Micro-emulsions, which are optically isotropic and thermodynamically stable systems of water, oil, surfactant, and/or co-surfactant, have been studied as drug delivery systems because of their capacity to solubilize poorly water-soluble drugs as well as their enhancement of topical and systemic availability. It helps to solubilize the lipophilic drug moiety and it shows rapid and efficient penetration to the skin. So it is beneficial for topical drug delivery[19]. For topical delivery micro-emulsion is incorporated in Carbool 934 gel base to prolong the local contact to the skin[20]. Number of medicated preparation is applied to the skin or mucous membrane that either enhances or restores a fundamental function of skin or pharmacologically alters an action in the underlined tissues. Such products are referred as topical or dermatological products. Many widely used topical agents like ointments, creams lotions have many disadvantages. They are sticky in nature causing uneasiness to the patient when applied, have lesser spreading coefficient so applied by rubbing and they also exhibit the problem of stability. 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. 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[2]. Hydrophobic drugs can be incorporated into emulgel using drug/oil/water emulsions. Most of the hydrophobic drugs cannot be incorporated directly into gel base because solubility acts 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 oil/water emulsion. The emulsion can be mixed into gel base. This may prove better stability and release of drug than simply incorporating drugs into gel base[2,21].

5. Formulation

5.1. For micro-emulsion

The concept of micro-emulsion was introduced first time in 1940 by Hoar and Schulman[7]. Micro-emulsion is clear, stable, isotropic mixture of oil, water and surfactant frequently in combination with co-surfactant[22]. Various ingradients that are part of micro-emulsion are listed in Table 1.

5.2. For emulgel

When both emulsion and gel are used in combined form, the dosage form prepared is named as emulgel. Various ingrdients that may be utilised in industry by one or the other way are listed in Table 2[23-27].

Table 1
Formula of micro-emulsion.

Name of ingradient	Example
Oil in which drug is soluble	Oleic acid, isopropyl myristate, labrafill M 1944 CS, soyabeen oil, cotton seed oil, olive oil *etc.*
Drug	Itraconazole, aceclofenac, nimesulide *etc.*
Surfactant	Tween 80, tween 60, tween 40, labrasol, cremophor RH-40 *etc.*
Co-surfactant	Ethanol, iso-butyl alcohol, acconam and iso-propyl alcohol, labraface lipofile, plurol oleique *etc.*
Aqueous phase	Water

Table 2
Formula for emulgel.

Name of ingradient	Example
Vehicle[23,24]	
Aqueous materials	Water, alcohol *etc.*
Oils	Arachis, cotton seed, maize oil *etc.*
Emulsifier[25]	Polyethylene glycol 40 stearate, sorbitan mono-oleate (span 80), polyoxyethylene sorbitan monooleate (tween 80), stearic acid, sodium stearate *etc.*
Gelling agent[26]	Carbopol-934/934P/940, HPMC 2910, sodium carboxymethyl cellulose, sodium alginate, xantham gum *etc.*
Penetration enhencer[27]	Oleic acid, lacithin, isopropyl myristate urea, linoelic acid, menthol, polypropylene glycol *etc.*
pH adjusting agent	Triethylamine, NaOH *etc.*

6. Method of preparations

First screening of oil, surfactant and co-surfactant for micro-emulsion is carried out. Solubility of drug is investigated in different oils, surfactants, and co-surfactants. Excess of the drug is added in 5 mL of each of oil with surfactant and co-surfactant. Surfactant and co-surfactant in screw-caped tubes was shaken on orbital flask at 100 r/min for 48 h at ambient temperature. The suspension is centrifused at 5000 r/min and clear supernated liquid is decanted and filter through 0.5 μm nylon membrane filter/ Whatman, the solubility of the drug is investigated by HPLC method[22]. A drug is dissolved in oil in which the drug has maximum solubility among the available, then surfactant and co-surfactant is added in which drug has maximum solubility, mixed well then water is added drop by drop and mixed well on magnetic stirrer. Transparent micro-emulsion is formed. Now any gelling agent (0.5%, 1% or 1.5% *etc.*) is suspended in water and hydrated for overnight. The pH is adjusted around 6 to 6.5 using triethanolamine. For preparation of micro-emulsion based emulgel, micro-emulsion and prepared emulgel are mixed in the ratio of 1:2, 1:1, 2:1 *etc*. or we can apply simplex lattice factorial design while preparing the same[20].

7. Characterization

7.1. Characterization of micro-emulsion

7.1.1. Viscosity

The viscosity is measured to determine the rheological properties of formulations. Viscometer Brookfield Rotational r type is used to measure the viscosity. Results are taken into triplicate and average is taken into consideration.

7.1.2. pH

The pH is measured by digital pH meter, results are taken into triplicate 7 then average of resuts are taken into consideration. The pH of Micro-emulsion is also required to measure because change in pH may affect the zeta poantial and finally affect the stability of the products.

7.1.3. Drug content

The drug content is measured by UV visible spectroscopic method[28].

7.1.4. Centrifugation

This parameter is measured to evaluate physical stability. The micro-emulsion is centrifused at 5000/min for 10 min to check system showing creaming or phase separation. The system is observed visually for appearance[29].

7.1.5. Conductivity

Electric conductivity of micro-emulsion is measured at ambient temperature with digital conductometer. Results are taken into triplicate and finally average is taken[30].

7.1.6. Dilution test

If continuous phase is added into micro-emulsion, it will not crack or separate into phases. A total of 50 to 100 times aqueous dilution of micro-emulsion are carried out and visually checked for phase separation and clearity. Results are taken into triplicate and finally average is taken[31].

7.1.7. Percent transmittance measurement

Micro-emulsion is diluted for 50 to 100 times. The percent transmittance of formulation is measured at λ_{max} using UV-visible spectrophotometer against water as blank. Results are taken into triplicate and finally average is taken[32].

7.1.8. Zeta potential and globule size analysis

Micro-emulsion is diluted for 50 to100 times. Globule size, size distribution and zeta potential of micro-emulsion are determined using dynamic light scattering technique by Malven Zetasizer (NANO ZS). Results are taken into triplicate and finally average is taken[4, 29].

7.1.9. Referective index

The referective index of micro-emulsion is measured by digital Abbe referectometer[33].

7.1.10. Osmolarity determination

The osmolarity of micro-emulsion is measured by following equation[34]:

mOsm/L= [Concentration (g/L)/molecular weight]×1000

7.2. Characterization of micro-emulsion based emulgel or microemulgel

7.2.1. Physical appearance

The prepared micro-emulsion based emulgel is inspected for the colour, homogenity, consistancy and pH. The pH of the 1% aqueous solution of the prepared micro-emulsion based emulgel is measured by pH digital meter.

7.2.2. Spreadability measurement

To determine the spreadability of micro-emulsion based emulgel, 0.5 g of emulgel is placed within circle of 1 cm diameter pre-marked on a glass plate, over which second plate is placed. A weigth of 500 g is allowed to rest on the upper glass plate for 5 min. The increase in diameter is observed due to emulgel, the spreading is noted[20].

7.2.3. Rheological study

Main viscosity is determined at 37 °C by means of Brookfield viscometer.

7.2.4. Drug content detemination

The Drug content in micro-emulsion based emulgel was measured by dissolving known quantity of micro-emulsion based emulgel in solvent (methanol) by sonication. Absorbance was measured after suitable dilution at λ_{max} using UV/VIS spectrophotometer.

7.2.5. Tube test (extractability test)

It is a usual empirical test to measure the force required to extrude the material from tube. The method adopted for evaluating micoemulsion based emulgel formulation for extrudability is based upon the quantity in percentage of gel and gel extruded from aluminum collapsible tube on application of weight in grams required to extrude at least 0.5 cm ribbon of emulgel in 10 seconds. The more quantity is extruded, the better extrudability is[35].

7.2.6. In vitro release study

Franz diffusion cell (with effective diffusion area 3.14 cm^2 and 15.5 mL cell volume) is used for the drug release studies. Microemulgel (1 g) is applied onto the surface of egg

membrane evenly. The egg membrane is clamped between the donor and the receptor chamber of diffusion cell. The receptor chamber is filled with freshly prepared phosphate buffer solution (pH 6.8). The receptor chamber is stirred by magnetic stirrer. The samples are collected at suitable time interval. Samples are analyzed for drug content by UV visible spectrophotometer at λ_{max} (nm) after appropriate dilutions. The cumulative amount of drug released across the egg membrane is determined as a function of time.

7.2.7. Skin irritation study

Formulation, 0.5 g of each is applied on the hair-free skin of rabbits by uniform spreading over an area of 4 cm^2. The skin surface is observed for any visible change such as erythema (redness) after 24, 48 and 72 h of the formulation application. The mean erythemal scores are recorded depending on the degree of erythema: no erythema=0, slight erythema (barely perceptible-light pink)=1, moderate erythema (dark pink)=2, moderate to severe erythema (light red)=3, and severe erythema (extreme redness)=4[36].

7.2.8. Syneresis measurement test

Upon standing sometimes gel system shrinks a bit and little liquid is pressed out. This phenomenon is known as syneresis. In this test, microemulgel is put in a cylindrical plastic tube with a perforated bottom which is covered with filter paper (Whatman No. 41). These tubes are then placed in centrifuge tubes and centrifuged for 15 min. The cylindrical plastic tube and liquid which had separated from microemulgel are weighted. The liquid which is separated from microemulgel is weighted. The percentage of syneresis is then calculated as the ratio of weight of liquid separated from the microemulgel to the total weight of microemulgel before centrifuegation and multiplied by 100. The data were reported as the average of five measurements[37].

7.2.9. Ex vivo study

In *ex vivo* study pharmacological action of active pharmaceutical ingredient is studied by inducing disease, diorder or infection in suitable animal and then comparing the effectiveness of formulation with placebo and market leader formulations is done[38].

7.2.10. Stability study

Samples of drug loaded microemulgel formulations are sealed in ampoules and then placed in stability chambers at different temperature conditions *i.e.*, room temperature condition [(25±5) °C, 60%±5% relative humidity] and accelerated condition [(40±5) °C, 75%±5% relative humidity] for 2 months. Duplicate samples are withdrawn at the 0, 1st and 2nd month to evaluate their physical and chemical stabilities. The physical stability is evaluated by visual inspection for physical changes such as phase separation and drug precipitation. Chemical stability is expressed as the content of drug determined by UV visible spectroscopic method at λ_{max} (nm)[39].

8. Conclusion

The drug loaded micro-emulsion based emulgel drug delivery system can be effective novel topical formulation for the fast relief from chronic condition. The micro-emulsion based emulgel gives two, three or four folds more action than normal marketed product, so that less dosage and dose frequency are required compareed to conventional drugs.Finally very less side effects occur and more acceptance is received from patient side.

Conflict of interest statement

We declare that we have no conflict of interest.

Comments

Background

Topical delivery systems for drugs make localized administration of the drug anywhere in the body. Formulations allows a wide variety of ingradients intended for cosmetic or dermatological application and can be formulated with varying physico-chemical properties, as solid, semisolid or liquid. Micro-emulsion of drug is prepared and incorporated into emulgel to prepare microemulgel.

Research frontiers

Micro-emulsion based emulgel novel topical drug delivery system has dual release control system. Micro-emulsions are micronized, thermodynamically stable systems having low interfacial tension with several features like enhanced permeability, good thermodynemic stability and prolong release. Emulgel prolongs the drug release, increases patient compliance and stability of emulsion.

Related reports

Micro-emulsion has more bioavailibility than any topical preparation while emulgel has patient compliance, good spreadability, thixotropic, easily removable, emollient and nonstaining features, and excellent consistancy compared with any type of topical preparations.

Innovations & breakthroughs

The combination of microemusion and emulgel have more bioavailibility than any other topical preparation. Moreover, it prolongs drug action, can be easily applied, and terminate medications whenever required. It is greaseless with good spreadibility and long shelf life as well.

Applications

Micro-emulsion based emulgel is most apllicable for both hydrophilic and hydrophobic drugs. The drugs with low bioavailibility are also subjected to the microemulgel to increase bioavailibilty.

Peer review

This is a good review article in which author try to provide topical formulation having advantages of both micro-emulsion and emulgel providing high biavailibility of drug. The drug loaded micro-emulsion based emulgel drug delivery system can be an effective novel topical formulation for the fast relief from chronic condition. The micro-emulsion based emulgel gives two to four folds more efficacy than marketed topical product, so that less dose and dose frequency is required.

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