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MICROEMULGEL: A NOVEL APPROACH FOR TOPICAL DRUG DELIVERY

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ABSTRACT

Topical drug delivery is mostly preferred for dermatological action. Topical dosage form such as cream, ointments, gels etc. has certain drawbacks like stability problems, stickiness, poor absorption as well as permeability. It has limitations in terms of drug solubility, residence time, lipophilicity and permeability. To overcome this, a novel approach microemulsion based gel is formulated. Microemulgel is topical drug delivery system that incorporates the properties of both gel and microemulsion and shows dual release control system. The microemulgel is prepared by reducing the globule size of the emulsion (less than 200nm) so that the drug particles can easily penetrate through stratum corneum. In spite of penetration, microemulgel has several advantages like easily spreadable, non-grease, thixotropic, transparent, and bio-friendly. Currently many drugs of antimicrobial, antifungal and non-steroidal anti-inflammatory class are studied for topical delivery through microemulgel formulation. After the brief study, it can be concluded that the microemulgel appear better and effective delivery system as compared to other topical drug delivery system.

INTRODUCTION

Topical drug delivery defined as the application of a formulation directly via skin to treat disorder with the advantages of avoiding first-pass metabolism and increasing the therapeutic efficiency of the drug [1]. Topical preparations produce localized effects at the site of their application into the underlying layers of skin or mucous membranes virtue of penetration. It provides flexibility to deliver drugs more effectively to a selective site. It provides utilization of drugs with a short biological half-life, narrow therapeutic window to increase the duration of action. The

topical drug can be administered anywhere in the body through ophthalmic, rectal, vaginal, and on skin as topical routes. The route of administration depends upon the type and severity of the disease. Drug delivery system can provide direct application of a formulation to the skin to get the localized effect of the drug. A topical drug delivery system has many advantages as they deliver drugs more selectively to a specific site. The reason for using topical delivery is to avoid GI incompatibility and metabolic degradation associated with oral administration.

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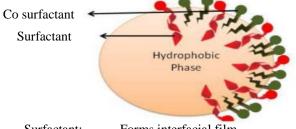
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Moreover, the topical delivery provides an increased bioavailability and consistent delivery of drug at extended-release rates from topical dosage form depending on physicochemical properties of the carrier and the drug [2].

The concept of microemulsion was introduced by Hoar and Schulman during the 1940's. Microemulsion contains water, oil, and amphiphilic which are an optically isotropic and thermodynamically stable liquid micro-dispersion. Microemulsion is the vehicle which improves the delivery, efficacy, and bioavailability of many drugs. "Microemulsion" refers to a thermodynamically stable and clear dispersion of two immiscible liquids; contain oil and water which is stabilized by surfactant molecules by forming interfacial film. A microemulsion is considered as a kinetically stable liquid dispersion of a lipid phase and an aqueous phase, with a surfactant. The dispersed particles having a size range of 5-200 nm, and have tiny oil/water interfacial surface tension [3].

Microemulsions are transparent because of their globule size (less than 25%). High energy input is not required in the formation of the microemulsion. In several cases, a co-surfactant is use additionally to the surfactant, the lipid phase, and therefore the aqueous phase. The microemulsion structure is mentioned below figure 1. There are three types of microemulsions are formed depending on the composition:

- 1. Oil in water micro emulsions in which oil phase is dispersed phase and water is continuous aqueous phase
- 2. Water in oil micro emulsions in which water phase is dispersed in the continuous oil phase;
- 3. Bi-continuous micro emulsions in which micro domains of lipid and aqueous phase are inter-dispersed in the system.



Surfactant: Co surfactant: Forms interfacial film
Ensure flexibility of interfacial layer

⇒ Reduce interfacial tension

Fig.1 Microemulsion Structure [3]

To stabilize the microemulsion suitable combination of surfactant and cosurfactant is necessary [4]. The main principle of this system is to form o/w type of micro-emulsion following

dilution by aqueous phase under gentle agitation. This microemulsion retains the drug in a dissolved form and small droplets size provide large interfacial area for drug absorption. Apart from solubilization, due to the presence of lipid in a formulation further helps to enhance the permeability of the drug.

When micro-emulsion as well as gels is used in combination to form microemulgel, they exhibit characteristics of both. Microemulgel helps to deliver the hydrophobic drugs by formulating oil in water microemulsion and this microemulsion can be incorporated into the gel base. They provide a larger area for absorption of drug and lipid portion intensify the bioavailability by better penetrability of drugs. Also, the gel base provides the better stability to micro-emulsion. In comparison to micro-emulsions, microemulgel have a firm degree of elegance and they are easily washable if required [5].

Advantages of Using Micro-Emulgel as a Topical Drug Delivery System

- ➤ Hydrophobic drugs can be easily incorporated into gels using o/w microemulsion.
- Better loading capacity.
- > Production feasibility and low preparation cost.
- ➤ No intensive sonication.
- > Controlled release.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.

Disadvantages of Microemulsion Based Gel

- ➤ The larger particle size drugs not easy to absorb through the skin.
- Poor permeability of some drugs through the skin.
- > Can be used only for drugs which require very small plasma concentration for action.
- Possibility of allergenic reactions.
- An enzyme in the epidermis may denature the drugs.
- > Skin irritation of contact dermatitis may occur due to drug or excipients [6].

FORMULATION CONSIDERATIONS Selection of Oil Phase:

The oil phase could consist of carrier oil in which the lipophilic bioactive compound is dissolved [7]. In microemulsion formulation, low molecular weight oils are preferred with respect to high molecular weight oils (i.e. triglycerides); they are

able to penetrate the interfacial film enhancing the formation of an optimal curvature of the interfacial film. Moreover, being thermodynamically stable system, microemulsions do not incur in instability phenomenon such as Ostwald ripening therefore, addition of oil as ripening inhibitors is not required [8]. The oil that shows excess solubility of drug is selected as an oil phase for formulating microemulsion based gel. The consistency of these lipids may range from mobile liquid to high solids. The lipid phase sometime acts as penetration enhancer therefore there is no need to add penetration enhancer in microemulsion delivery system [9]. Researcher shows that the soyabean oil in a system composed of water, essential oils (EOs) and Tween 80. Soybean oil was able to improve the dilutability of EOs-based microemulsions and it had a great impact on the formation of the system, expanding the regimes of microemulsions and reducing the droplet size. It contributed to reduce the EOs volatility as well [10].

Selection of Surfactants:

The second criteria for the choice of surfactants were supported their ability to make microemulsion with designated lipid having the very best solubility for drug [11]. Surfactants are unit active molecules that have each a hydrophilic and a lipotropic domain in their molecular structure [12]. Because of their amphiphilic nature, surfactants enable the dispersion of two incompatible phases lowering the surface tension up to get enough versatile film ready to deform round the droplets with the best curvature [13]. Throughout the emulsification method, they are quickly absorbed within the interface and stop the droplets' aggregation [14]. The non-ionic, zwitterionic, cationic, or anionic surfactants are used to stabilize such systems. Ionic and non-ionic surfactant is effective to the extent of the microemulsion region. Example of non-ionic embodies polyoxyethylene surfactants like Brij 35, tween20/80, or sugar esters like sorbitan monooleate (Span 80) [15]. Zwitterion is notable example phospholipids.

Microemulgels are combination of two dosage form such as microemulsion and gel, the microemulsion is either oil in water or water in oil that are gelled by adding gelling agent to it, as compared to microemulsion, emulsions are thermodynamically unstable but addition of emulsifying agents make them stabilize at some extent by reducing its surface tension. A satisfactory surface-active agent provides the balance between hydrophilic & lipotropic teams & capable of formulating stable emulsions. Spans and tweens are nonionic surfactants having HLB values

more than eight and area units utilized in the formulation of o/w emulsions whereas mineral oils like liquid paraffin have HLB values less than eight & so area unit utilized within the formulation of water in oil emulsions [16].

Selection of Co-surfactants:

Cosurfactants are generally short and medium-chain alcohols and polyglycerol derivatives, including ethanol, isopropanol, isopropyl myristate, and propylene glycol (PG). Nonionic surfactants have also been used to provide low irritancy cosurfactants [17]. The cosurfactants with surfactant are used to decrease the interfacial tension to transient negative value. At this negative value, fine droplets are formed due to the interface expansion and more surfactant/cosurfactant get adsorbed on the surface until the bulk condition is depleted enough to make the interfacial tension positive again. Cosurfactant of short-medium chain length alcohols also ensures that the interfacial film is flexible enough to deform readily around droplets, as the interaction between primary surfactant molecules decreases both the polar head group interaction and hydrocarbon chain interaction [18]. Polyethylene glycol derivatives of stearoyl phosphatidyl ethanolamine, ethanol, fatty acid esters of propylene glycol, and oleic esters of polyglycerol, ethyl glycol, and propylene glycol were also evaluated as cosurfactant in microemulsion drug delivery system [19].

Selection of Gelling agent:

The gel structure is providing in formulation via adding gel phase. Natural and artificial are of two varieties. Incorporation of gel phase to a formulation makes it thixotropic [9]. The thickening agents are utilized in O/W microemulsions and nanoemulsions to match the density of the oil part with the encompassing liquid part. Thus, engaged on the impact of attraction forces, they may retard the incidence of creaming or deposit phenomena [20]. Moreover, texture modifiers are widely used likewise. Generally, water-based systems have to be compelled to contain a preservative agent to avoid the proliferation of microorganisms. Within the specific case of EObased systems, the addition of preservatives is typically extra since EOs is naturally occurring antimicrobials. The study shows that the exploited EOs-based microemulgel to encapsulate nisin, an antimicrobial agent. Rosemary, thyme, oregano, and herbaceous plant Eos were elite to boost the system's overall antimicrobial activity, through a synergistic impact of nisin and EOs [21]. Research shows that to prepare nanoemulgel of Amophotericin B carbopol 980 was used as a gel base and will economical, stable, and safe carrier for increased and sustained topical delivery for Amophotericin B in native skin mycosis [22].

Pseudo-ternary phase diagram:

The water titration method is used to construct phase diagrams to identify the type of structure that resulted within the following emulsification and to characterize the behavior of mixtures on dilution [23]. Pseudo-ternary phase diagram of oil, water and surfactant/cosurfactant mixture are constructed at fixed weight ratio of surfactant/cosurfactant. The emulsification region is obtained by mixing ingredients into the vial and titrates with water. Formation of monophasic and biphasic system is confirmed by visual inspection. In case of monophasic system, clear and transparent mixtures are visualized after stirring and in case of biphasic system turbidity appeared followed by phase separation. Exclusively the region, where clear microemulsion was considered. Then the prepared microemulsion were analyzed for particle size and polydispersity index (PDI) [24]. Theoretical regions of microemulsion system of oil (O), water (W), and surfactant+cosurfactant (S) are represented in figure 2.

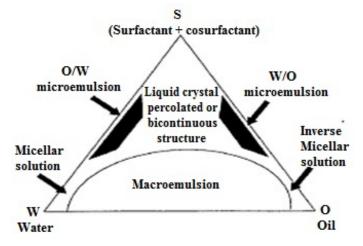


Fig.2 Hypothetical phase regions of microemulsion system of oil (O), water (W), and surfactant + cosurfactant (S) [2].

FORMULATION METHODS OF MICROEMULGEL

Microemulgel may be developed with 3 steps [25].

Step 1: Preparation of oil in water or water in oil microemulsion using oil phase and water phase.

Step 2: Preparation of gel using gelling agent and water by constant stirring and optimization of pH.

Step 3: Incorporation of microemulsion into the gel base to formulate microemulgel [26, 27].

For the preparation of microemulsion essentially 2 strategies i.e. low energy and high energy emulsification techniques are used.

Low energy emulsification technique:

Low energy technique benefits over high energy strategies for the formulation of the microemulsion. The low energy technique includes the phase inversion technique and the spontaneous technique. The phase inversion technique involves the blending of oil, water, and wetting agent in a much-predefined ratio. The oil phase is titrated with aqueous phase at constant stirring, therefore the formation of nanosized drop during a continuous phase.

The addition of wetting agent & co-surfactant affects the emulsification method. The amount of wetting agent used in the formulation determined which kind of emulsion is formed; the temperature plays an important role in the formation of emulsion.

At low temperatures, they are hydrophilic and oil in water type. At higher temperatures, they are lipophilic and water in oil type. At associate degree intermediate temperature, microemulsion happens with the aqueous phase & oil part to make a bicontinuous structure.

The spontaneous technique is specially used for the unstable element or else, a temperature-dependent spontaneous twist of non-ionic wetter is employed for activity throughout the part inversion technique.

The emulsions fashioned at part inversion temperature are going to be reversed on cooling with continuous stirring. This method is additionally restricted to include the unstable element, though limitation takes as approach reduced part inversion temperature by appropriate choosing surfactant [28].

High energy emulsification technique:

Apply high shear force energy to rupture the interior introduce the nanosized drop by hard hitting homogenizers, ultrasonicator. In this technique the external energy is required to stabilize the formulation [29].

EVALUATION OF MICROEMULSION

Droplet size microemulsion:

Globule size distribution of microemulsion is set by using particle size analyzer.

Zeta potential measure:

Zeta potential is used to determine the charge on the drop. In an exceedingly standard emulsion, the charge on oil droplets is negative because of the presence of fatty acids.

Viscosity:

The viscosity of prepared microemulsion is to be determined by Brookfield viscometer [30].

Centrifugation

It is used to measure the physical stability of microemulsion centrifuge at 5000 rpm for 10 min at close temperature and value for creaming and phase separation visually. Conductivity measure offers a plan concerning the sort of microemulsion if fashioned, whether or not it is oil in water or water in oil emulsion visually [31].

EVALUATION OF MICROEMULGEL

Physical Examination:

The prepared microemulgel formulations are visualized for their physical appearance such as color, texture, phase separation, homogeneity and pH [32].

Spreadability Study:

The efficacy of microemulgel depends on spreading. The spreading help in the application of gel to the skin, therefore the prepared microemulgel should have good spreadability.

A required amount of gel is placed within a circle of 1cm diameter which is premarked on a glass plate, above which another glass plate is placed, to estimate the spreadability. A weight of 500 gm is permitted to rest on the upper glass plate for 5 min. The increase within the diameter spreading was noted and calculates using formula:

$$S = \frac{M \times L}{T}$$

M – Weight tied on upper slide;

L – Length of glass slide

T – Time in seconds

Extrudability Study:

It is the ability of microemulgel to be squeezed out of nozzle from collapsible tube in a continuous manner. A closed collapsible tube containing microemulgel is pressed firmly at crimped end and a clamp is applied to put off any roll back. The closure of the tube is detached and then the microemulgel was extruded out. Then the quantity of the extruded-out gel is weighed and calculated.

Extrudability

 $= \frac{weight applied to produce microemulgel om tube (gm)}{area (cm^2)}$

Drug content determination:

The drug content of microemulgel is measured using spectrophotometer by dissolving known quantity of microemulgel in a suitable solvent and sonicated to combine well. The absorbance of sample and standard are measured at given wavelength [33].

In-vitro diffusion study:

In-vitro drug release is enforced by Franz diffusion cell (diffusion area 3.14 cm² and 15.5 ml cell volume). Microemulgel is applied to the surface of the membrane uniformly. The membrane is compressed between the donor and therefore the receptor chamber. The receptor chamber is filled with suitable solvent. The samples are collected and examined for drug content by ultraviolet light spectrophotometer at relevant wavelength once acceptable dilutions. The cumulative amount of drug release across membrane is determined as a function of time.

Microbiological assay:

Ditch plate technique is used. The nutrient agar media is prepared and allowed to set at room temperature. The bacterial cell suspension is inoculated over the surface of the medium using sterile cotton swab. Gellified emulsions are placed in an exceedingly ditch cut within the plate. The plate is then incubated in the anaerobic jar at temperature 37°C for 48 h. The zone of inhibition is measured and diameter is recorded.

Stability studies:

The prepared microemulgel are subjected to stability studies at following parameters 5°C, 25°C/60% RH, 30°C/65% RH, and 40°C/75% RH for a number of 3 months. Samples are withdrawn at 15-day time intervals and assessed for the physical appearance, pH, rheological properties, drug content, and drug release profiles [2].

FUTURE PROSPECTIVE

The hydrophobic nature of some medications is the major drawback for formulation and development. The most disadvantage of hydrophobic medication is its poor water solubility and bioavailability. The delivery of such a reasonable drug within the biological system could be a difficult task. Out their topical preparations like ointment, cream, and lotion have several disadvantages. They are sticky in nature inflicting uneasiness once applied, even have less spreadability and use with rubbing, they exhibit the matter of stability conjointly. The employment of gels has expanded each in cosmetics and in pharmaceutical preparation. A gel could be a solid preparation, that is immobilized by the physical phenomenon and a molecule network of fibers engineered from a low quantity of a gelatin substance. In spite of the various blessings of gel, it's a significant downside to the delivery of hydrophobic medication. So, the small emulsion-based gel is employed to defeat this.

CONCLUSION

Microemulgel is considered as a best approach for topical delivery as it has many favourable properties such as easily spreadable, easily removable, biofriendly and has longer shelf life. Microemulgel has ability to deliver hydrophobic drug by incorporating microemulsion into the gel base which provide the benefit of both. Currently, hardly few marketed microemulgel formulations are available in market however; it offers a vast field for development and research. Microemulgel offer a wide utility in dermal care in future.

FINANCIAL ASSISTANCE Nil

CONFLICT OF INTEREST

The authors declare no conflict of interest.

AUTHOR CONTRIBUTION

Priya Kushwah, Sweta S Koka, Ashish Gupta and Ravi Sharma collected the content and performed the extensive review of available literatures. Pravin K Sharma and G N Darwhekar contributed to drafting and revising the manuscript. All the authors framed the final manuscript.

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