

Formulation and Evaluation of Antifungal Nanoemulsion Gel for Topical Application.

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ABSTRACT: The aim of present study is formulation and evaluation of Antifungal nanoemulsion gel of the poorly water soluble drug. Topical nanoemulsion gel drug administration is a localized drug delivery system anywhere in the body through Skin, Oral, ophthalmic, vaginal as topical routes. Nanoemulsion gel provides better drug loading capacity, stability, permeability and bioavailability as compared to cream ointments. Both hydrophilic and hydrophobic drugs can be delivered by using nanoemulsion based gel formulation. When gels and Nano emulsions are used in combined form the dosage form are referred as nanoemulsion based gel. It is formulated by mixing an oil-in-water type or water-in-oil type emulsion with a gelling agent. Mostly The nanoemulsion gels are used as analgesics and antifungal agents.

KEYWORDS: Antifungal Nanoemulsion gel Bioavailability, Hydrophobic drugs, Topical drug delivery

I. INTRODUCTION:

Topical drug delivery is the best route to deliver the drugs having more side effects orally. Nano emulsions are colloidal dispersions composed of an aqueous phase, oil phase, surfactant and co-surfactant at appropriate ratios. Nano emulsion have low interfacial tension as compared to coarse Emulsion. The size of dispersed phase droplet is very small, usually below 10-200 nm in diameter, due to its very small droplet size, nanoemulsion gel becomes transparent. Nano emulsions can be used to deliver drugs to the patients via several routes, but the topical application of nanoemulsion in the form of gel has gained increasing interest. nanoemulsion gels very good carrier for topical delivery of highly lipophilic drugs. Drug

concentration can be reduced due to lack of metabolic degradation of drug before reaching the targeted site. Conventional topical dosage forms like ointments, Creams, Gels shows Fluctuation in bioavailability.

Normally gels deliver only the hydrophilic drugs, similarly Ointments deliver only hydrophobic drug, So to deliver both Hydrophobic and Hydrophilic drugs the Novel approach i.e nanoemulsion Gel formulations are used. This nanoemulsion gel formulation improves Properties for patient compliance. Several antifungal formulations are available in the market like cream, gel, lotions powders, ointment etc. but the nanoemulsion gels becomes more convenient and acceptable to patient.

Structure of Skin:

The skin of adult human body has average surface area of 1.8 m², which contain average 200-300 sweat ducts and 40-70 hair follicles on sq. cm of the skin. Skin pH varies from 4 to 5.6 which depends on secretion from the sweat glands. Cutaneous membrane of skin is divides into 3 parts,

1. Epidermis
2. Dermis
3. Hypodermis



a. Epidermis

Epidermis is the outer most layer of the skin, containing stratified squamous epithelium which has stratum basale - deepest layer and stratum corneum - superficial layer. Stratum corneum, which is the outermost layer of skin, hard in nature due to the process of keratinisation and act as physical barrier to most drugs, SC composed of 10 to 20 cells layers. Cell of Subcutaneous layer are flat and plate-like with 2500 μm wide, 34-44 μm long, 0.5 to 0.20 μm thick. Lipid content of SC includes glycosphingolipid, a neutral lipid, cholesterol sulphate, phospholipids, and keratin as protein. Stratum basale lies between the SC and the dermis having thickness of 50-100 μm . Cells Structure of this layer are similar to other living tissue. The water content of this layer is about 90% and mainly contains melanin and langerhans cells .

b. Dermis/Corium

Deeper and thicker (2000 to 3000 μm) region under the epidermis is called dermis, mostly contracted with structural fibrin and very few cells same as found in normal tissue. Dermal papillae are the outer most layer having signalized projection. It also contains oil-secreting glands, sweat glands, hair follicles and nerve ending. Elastic and collagenous fibers within dermis provides starchability and tone to the skin. The density of its fibre meshwork, and therefore its physical properties, varies within an area, in different parts of the body, and with age and gender.

c. Hypodermis

The hypodermis, composed of loose connective tissue varies in thickness, merges with the lower part of the dermis. Apart of this it also composed of secretary sweat glands, fibrous tissue containing blood vessels nerve ending , and cutaneous nerves. Many consider that drug get

absorbed into the systemic circulation without passing through this layer by means of blood vesicles and sweat ducts.

Fungal Infection:

Any disease caused by fungus is called as fungal infection. A fungal infection, also called as **mycosis**, is a skin disease caused by a fungus. There are millions of species of fungi. They live in the dirt, on plants, on surface of floor, and on your skin. occasionally, they can lead to skin problems like rashes or bumps

Following are the types of fungal diseases causes by infectious Fungus

- Ringworm of the body (tinea corporis).
- Athlete's foot (tinea pedis)
- Jock itch (tinea cruri)
- Ringworm of the scalp (tinea capitis)
- Tinea versicolor.
- Cutaneous candidiasis
- Onychomycosis (tinea unguium)

Various types of Topical antifungal formulations are available in market like creams , gels , Ointments . Now a days Nanoemulsion based Gel becomes more acceptable , more convenient formulation.

Advantages of Nanoemulsion Gel

The Nanoemulsion gel have various advantages which are:

- Easily acceptable to patients
- Suitable for self medication
- Avoids first pass metabolism
- Target specific action
- Increase the rate of absorption
- Increase bioavailability
- Less amount of energy required
- Helpful to mask taste
- Lipophilic drugs can be easily gel soluble

Disadvantages of Nanoemulsion Gel

- Large concentration of surfactants and cosurfactants are required to stabilise the nanoemulsion
- Stability influenced by environmental temperature , pH

Components of Nanoemulsion Gel

- **Oils** : generally mineral oils are used as vehicle for drug E.g castor oil , rose oil, clove

oil, eucalyptus oil, corn oil, sunflower oil, sesame oil, fish oil.

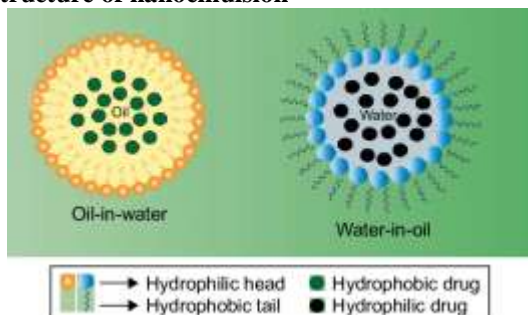
- **Aqueous phase** : distilled water is used as aqueous phase
- **Surfactants and co-surfactant**: surfactants are used to reduce surface tension and to increase solubility of drugs. Selection of surfactant depends upon type of emulsion. Commonly used surfactants are Span 80, Tween 80, sodium stearate, Captex, Labrasol etc
- **Gelling agents** :

Gel forms polymer network. Commonly used gelling agents are E.g Agar, guar gum, HPMC, tragacanth, carbapol

- **Permeation enhancer** :

It increases the permeability of skin for transport of drug through skin. Commonly used permeation enhancers are Eucalyptus oil, Lecithin, Oleic acid, Urea, Chenopodium Linoleic acid oil, Isopropyl myristate.

Structure of nanoemulsion



Methods Of Preparations Of Nanoemulsion Gel

Nanoemulsions are prepared in following two steps

- 1) Preparation of Nanoemulsion
- 2) Addition of Nanoemulsion into gel

1) Preparation of nanoemulsion

Nanoemulsion can be prepared by following methods.

A) High pressure homogenization

This is highly efficient method of preparation of nanoemulsion in which forcefully introduction of oil and water along with surfactants, cosurfactants are passed through a small orifice at high pressure. Firstly, emulsion is formed with large volume fraction of dispersed phase, which may be diluted later on. Excess amount of surfactants are added to avoid coalescence.

B) Sonication

It is widely used method in which probe sonicator is placed in the mixture oil and water with

surfactants, cosurfactants to give mechanical force by which dispersion is converted into small sized droplets.

C) Microfluidisation

In this method water and oil are introduced through small orifice by pressure pump from opposite direction into mixing area, where they mixed with other high shear and converted into small droplets which in turn used to prepared nanoemulsion.

D) Spontaneous emulsification method

In the solution of oil and surfactant water is added at constant temperature and mixed lightly to produce o/w nanoemulsions. The preparation of nanoemulsion depends on surfactant structure, concentration of surfactants, interfacial tension, interfacial and bulk viscosity, phase transition region

E) Solvent displacement method

In this method nanoemulsions can be prepared by pouring the organic phase containing oil dissolved in a solvent into aqueous phase having surfactants at room temperature. The preparation of nanoemulsion occurs by diffusion of organic solvent, evaporated by vacuum. Small sized droplets of nanoemulsion can be prepared by taking appropriate ratio of solvent to oil.

2) Addition of nanoemulsion into gel

Gel base is prepared using gelling agent in a required quantity of water. After complete swelling and dispersion of gelling agent during 24 hours period, prepared nanoemulsion is slowly added under continuous stirring. Triethanolamine is added to gives homogeneous gel dispersion. Finally remaining part is adjusted with distilled water Figure.

Evaluation Of Nanoemulsion Gel:

• Physicochemical parameters

The prepared Nanoemulsion gel formulations are checked visually for their color, homogeneity, consistency and phase separation.

• Measurement of pH:

1gm of Gel is dissolved in 10ml water and pH is measured by digital pH meter. The pH range for topical preparation should be near to the neutral pH.

• Swelling Index:

1 gm of prepared nanoemulgel is taken on porous aluminium foil which is then placed on 10 ml of 0.1 N Sodium Hydroxide solutions. The sample ejected

time to time and weight is noted till no further variation in weight:

$$\text{Swelling Index (SW) \%} = \left[\frac{W_t - W_0}{W_0} \right] \times 100$$

Where, (SW) % = Percentage swelling,

W₀ = Original weight of nanoemulgel

W_t = Weight of swollen nanoemulsion gel at time t.

- **Measurement of viscosity:** Viscosity of nanoemulsion gel is measured by using Brookfield Viscometer

- **Skin irritation test:**

The nanoemulsion gel is applied on the shaven skin of rat and undesirable changes in color, change in skin layer should be checked up to 24 hours. If no irritation occurs after application nanoemulsion gel then the test is passed.

- **Drug Content:**

1% dilution of emulsion gel is done with suitable solvent and filtered through the whatman filter paper. 1 ml filtrate is then further diluted to 10ml, then the sample is analyzed by using UV spectrophotometer against blank and absorbance is noted

- **Dilution test:**

1% Aqueous dilution of Nanoemulsion Gel is done by adding continuous phase and visually checked for any separation in phase.

- **Refractive index:**

Refractive index of nanoemulsion Gel is measured by using Abbes refractometer.

- **In-vitro Diffusion studies**

Franz diffusion cell apparatus is used to perform diffusion study of prepared Nanoemulgel.

- **Spreadability Test:**

The therapeutic efficacy of nanoemulsion gel depends on its spreading value. For the determination of spreadability of nanoemulsion, 1gm of nanoemulsion gel is placed within the circle of 1cm diameter premarked on glass plate, in which second glass plate is placed. A 500g weight is allowed to rest on the upper glass plate for 5 min. The increase in diameter due to spreading of gel is noted.

- **Stability Study:**

As given in ICH guidelines, the formulations are stored in oven at 37±2°C, 45±2°C and 60±2°C differently for 3 months. Drug content is analysed every two weeks by suitable analytical method. Any change in physical and chemical properties are observed.

II. CONCLUSION:

Topical nanoemulgels have proven as better option for effective and convenient delivery of Both hydrophilic and hydrophobic drugs. More patient compliance due to its non greasy property. Incorporation of nanoemulsion into gel makes formulation dually control released system, Creaming, phase separation problems associated with classical emulsion get resolved. It increases drug solubility, increase bioavailability and reduce patient variability. Nanoemulsion gel formulations are more effective for treatment of **fungal infections**, pain, Inflammation and other topical disorders. Due to the small globule size, the Nanoemulsion gel can be easily penetrate through the skin and hence it also treat systemic infections.

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