RIZATRIPTAN BENZOATE NANOEMULGEL FOR TOPICAL DRUG DELIVERY SYSTEM: REVIEW

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Abstract

Drug delivery through the skin to the circulation is convenient for variety of clinical conditions because of which there has been a substantial interest during this area. It offers the advantage of steady state controlled drug delivery over extended periods of your time, with self- administration also being possible, which cannot be the case with parental route. The drug input may be eliminated at any time by the patient just by washing off the applied dosage. an additional advantage is that the total absence of gastrointestinal side effects like irritation and bowel ulcers which are invariably related to oral delivery. Topical delivery has been developed for variety of disease and disorders. The treatment of skin diseases additionally as musculoskeletal disorders may well be advantageous from topical administration obtaining a substantial reduction in oral side effects with improved patient compliance. Many anti-inflammatory drugs are poorly water soluble and Nano suspension is that the techniques which is employed to enhance this characteristic, so anti-inflammatory drugs are chosen as a model for this study. Rizatriptan is employed to treat migraines. It helps to alleviate headache, pain, and other migraine symptoms (including nausea, vomiting, and sensitivity to light/sound). Prompt treatment helps you come back to your normal routine and should decrease your need for other pain medications. Rizatriptan belongs to a category of medicine called triptans. It affects a specific natural substance (serotonin) that causes narrowing of blood vessels within the brain. It's going to also relieve ache by affecting certain nerves inside the brain. Rizatriptan don't prevent future migraines or lessen how often you get migraine attacks the improved adoption of topical medication in current years has been impressive. this can be largely thanks to the very fact that the medication has proven to own more advantages than drawbacks.

Keyword: NanoEmulgel, Rizatriptan, Migraine

1.INTRODUCTION

1.1 Topical Drug Delivery System

Topical drug delivery system could be a route of administration of medicine via the skin to produce topical therapeutic effects. As skin is one in every of the most important and most superficial organs within the shape, pharmacists utilise it to deliver various drugs. This technique usually provides an area effect on certain positions of the body. In past, people used herbs to place on wounds for relieving the inflammatory effect or as pain relievers. the utilization of topical drug delivery system is far broader now, from smoking cessation to beauty purposes. Nowadays, there are numerous dosage forms which will be used topically, including cream, ointment, lotion, patches, toilet powder and far more.[citation needed] There are many advantages for this drug delivery system - avoiding first pass metabolism which might increase its bioavailability, being convenient and straightforward to use to an oversized area, being easy to terminate the medication and avoiding gastro-intestinal irritations. of these can increase the patient compliance. However, there are several disadvantages for this method - causing skin irritations and symptoms like rashes and itchiness may occur.

Topical formulation has mainly three functions:

- To help hydrate the skin because of their emollient properties.

- To protect from external environment or heal an intact or injured area of the skin.
- To deliver medication to the skin.

1.1.1 Classification of Topical Drug Delivery System

Liquid Preparation	Semi-solid Preparation	Solid Preparation	Miscellaneous
Liniments	Ointments	Topical Powders	Transdermal Drug Delivery system
Lotions	Creams	Poultices	Tapes and Gauzes
Paints	Pastes	Plasters	Rubbing Alcohols
Topical Solution	Gels		Liquid Cleaner
Topical Tinctures	Poultices		Topical Aerosols

Table 1: Classification of Topicals

1.1.2 Advantages of Topical Drug Delivery System

a) Avoidance of first pass metabolism.
b) Convenient and easy to apply.
c) Avoidance of the risks and inconveniences of intravenous therapy and of varied
d) Conditions of absorption like pH changes, presence of enzymes, gastric emptying time. Ability to easily terminate the medications, when needed.
e) Ability to deliver drug more selectively to a specific site.

1.1.3 Disadvantages of Topical Drug Delivery System

a) Skin irritation on contact dermatitis may occur due to the drug and/or excipients.
b) Poor permeability of some drugs through the skin.
c) Possibility of allergenic reactions.
d) Drugs of larger particle size not easy to absorb through the skin

1.2 Skin as Site for Drug Delivery

Most of the topical formulation is meant to be applied to the skin. So basic knowledge of the skin and its physiology function are important for designing topical dosage form. The skin of a mean form covers a area approximately 2m2 and receives about one third of the blood circulating through the body. a mean human skin surface is thought to contain, on the typical 40-70 hair follicles and 200-300 sweat ducts on every square centimeter of the skin. The pH of the skin varies from 4 to five.6. Sweat and carboxylic acid secreted from sebum influence the pH of the skin surface. The skin are often considered to own four distinct layers of tissue as shown in fig. 01.

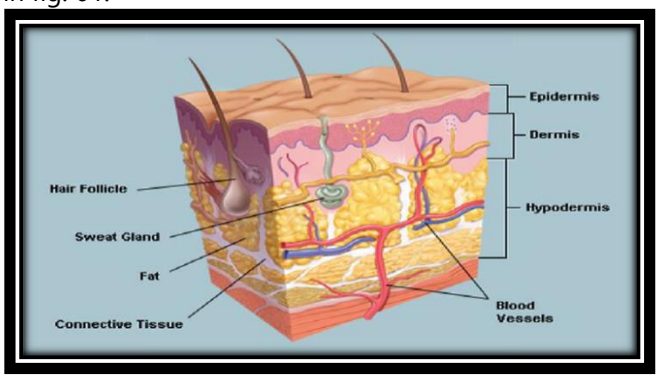


Fig. 01: Structure of Skin

1.2.1 Physiology of Skin

a) Non-viable epidermis
b) Viable epidermis
c) Viable dermis
d) Subcutaneous connective tissue

a) Non-viable epidermis:
Stratum corneum is that the outer most layer of skin, which is that the actual physical barrier to most substance that comes in touch with the skin. The corneum is 10 to twenty cell layer thick over most of the body. Each cell may be a flat, plate like structure 34-44 µm long, 25-36 µm wide, 0.5 to 0.20 µm thick - with expanse of 750 to 1200µm stocked up to every other in brick like fashion. stratum consists of lipid (5- 15%) including phospholipids, glycosphingo lipid, cholesterol sulfate and neutral lipid, protein (75-85%) which is principally keratin.

b) Viable epidermis:
This layer of the skin resides between the horny layer and therefore the dermis and encompasses a thickness starting from 50-100 µm. The structures of the cells within the viable epidermis are physiochemically almost like other living tissues. Cells are held together by tonofibrils. The density of this region isn't much different than water. The water content is about 90%.

c) Dermis:
Just beneath the viable epidermis is that the dermis. it's a structural fibrin and extremely few cells are prefer it may be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of loose animal tissue composed of fibrous protein embedded in an amphorphose ground substance.

d) Subcutaneous connective tissue:
The subcutaneous tissue or hypodermis isn't actually considered a real a part of the structured animal tissue which consists of loose textured, white, fibrous animal tissue containing blood and lymph vessels, secretary pores of the exocrine gland and cutaneous nerves. Most investigators consider drug permeating through the skin enter the vascular system before reaching the hypodermis, although the fatty tissue could function a depot of the drug.

1.2.2 Drug delivery across skin:

The epidermis is that the most superficial layer of the skin and consists of stratified keratinized squamous epithelium which varies in thickness in several parts of the body. it's thickest on with elastic fibers. The skin forms a comparatively waterproof layer that protects the deeper and more delicate structures. Blood vessels are distributed profusely beneath the skin. Especially important may be a continuous venous plexus that's supplied by inflow of blood from the skin capillaries. Within the most exposed areas of the body-the hands, feet, and ears blood is additionally supplied to the plexus directly from the little arteries through highly muscular arteriovenous anastomoses. a novel aspect of dermatological pharmacology is that the direct accessibility of the skin as a organ for diagnosis and treatment. The skin acts as a two way barrier to forestall absorption or loss of water and electrolytes. There are 3 primary mechanisms of topical drug absorption: transcellular, intercellular, and follicular. Most drugs withstand the torturous path around corneocytes and thru the lipid bilayer to viable layers of the skin. The following commonest (and potentially beneath recognized within the clinical setting) route of delivery is via the pilosebaceous route. The barrier resides within the outer most layer of the epidermis, the horny layer, as evidenced by approximately equal rates of penetration of chemicals through isolated stratum or whole skin. Creams and gels that are rubbed into the skin are used for years to deliver pain medication and infection fighting drugs to an affected site of the body.

1.2.3 Factors affecting topical absorption of drug

A) Physiological factor
a. Skin thickness
b. Lipid content
c. Density of hair follicles
d. Density of sweat glands
e. Skin pH

B) Physiochemical Factors
a. Partition coefficient
b. Molecular weight (<400 Dalton)
c. Degree of ionization (only unionized drugs gets absorbed well)
d. Effect of vehicles

1.2.4 Factors to be considered when choosing a topical preparation [

a) Irritation or sensitization potential. Generally ointments and w/o creams are less irritating while gels are irritating, Ointments don't contain preservatives or emulsifiers if allergy to those agents is concern.

b) Match the kind of preparation with the kind of lesions. as an example, avoid greasy ointments for acute weepy dermatitis.

c) Match the kind of preparation with the location (e.g. gel or lotion for hairy areas).

d) Effect of the vehicle e.g. an occlusive vehicle enhanced penetration of the active ingredient and improves efficacy.

1.2.5 Drug Penetration Routes:

There are two possible routes of drug penetration across the intact skin, namely the transepidermal and transappendegeal pathways, which are diagrammatically presented. The transepidermal pathway involves the passage of molecules through the horny layer; an architecturally diverse, multi-layered and multi-cellular barrier Transepidermal penetration is termed intra- or inter-cellular. The intra-cellular path through corneocytes, terminally distinguished keratinocytes, allows the transport of hydrophilic or polar solutes. Transportation via inter-cellular spaces allows diffusion of lipophilic or non-polar solutes through the continual lipid matrix. The transappendegeal route involves the passage of molecules through sweat glands and across the hair follicles.

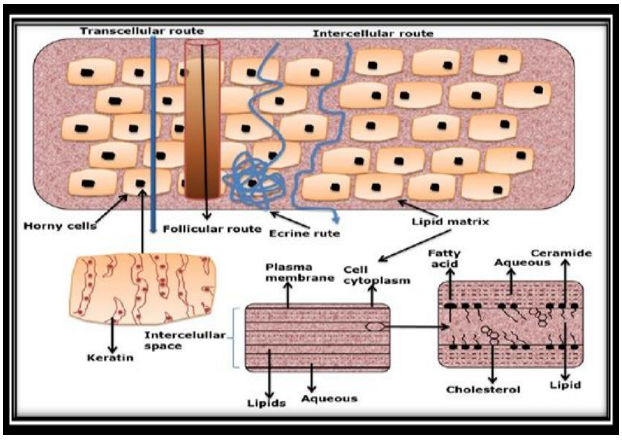


Fig 02: Possible drug penetration routes across human skin.

1.3 Emulsion

Emulsions are two-phase preparations during which one phase (the dispersed or internal phase) is finely dispersed within the other (continuous or external phase). The form can have either a hydrophobic-based (oil-in-water), or be aqueous based (water-In-oil). Because there are two incompatible phases in close conjunction, the physical stabilizing system. In most pharmaceutical emulsions, the stabilizing system Comprises surfactant (ionic or nonionic), polymers (nonionic polymers, polyelectrolytes, or biopolymers) or mixtures of those.

1.3.1 Types of emulsion

The emulsion is split into mainly two types, depending upon whether the continual phase is aqueous or oily.

a) Oil-in-water (o/w)

b) Water-in-oil (w/o)

Emulsions are of various types betting on the dimensions of droplets or nature of distribution.

a. Macroemulsion

hese are most typical form of emulsions where the particle size of droplets is quite 400nm. They're visually opaque but the individual droplets will be easily observed under microscope. Macro emulsion is thermodynamically unstable, but are often stabilized using surface active agents.

b. Microemulsion

Microemulsions are thermodynamically stable isotropic systems during which two immiscible liquids (water and oil) are mixed to create one phase by means of an appropriate surfactant or its mixture.

c. Nanoemulsion

The term 'Nanoemulsion' refers to a thermodynamically stable isotropically clears dispersion of two immiscible liquids, like oil and water stabilized by an interfacial film of surfactant molecules. Nanoemulsion is taken into account to be a thermodynamically or kinetically stable liquid dispersion of an oil phase and water innovate combination with a surfactant. The dispersed particles droplet size is a smaller amount than 100 nm.

1.3.2 Constituents of emulsion

a. Active ingredient:

i.e. drug.

b. Oil phase: Various mineral oils or synthetic oils are used as oil phase. e.g. Castor oil, liquid paraffin, Arachis oil, Capmul oil.

c. Aqueous phase:

It consists of water or alcohol.

d. Emulsifier:

Various emulsifying agents like tween, span, polyethylene glycol, Sodium sterate, etc are used as emulsifying agents to stabilize the emulsion.

e. Preservatives:

Various antimicrobial preservatives are utilized in the pharmaceutical formulation like e.g. Propyl paraben, Methyl paraben, Benzalkonium chloride, carboxylic acid, Benzyl alcohol etc.

f. Antioxidants:

Various antioxidants are employed in the emulsion to stop the rancidity of the formulation e.g. Butylated Hydroxy Toluene (BHT), Ascorbyl palmitate, Butylated hydroxyl anisole (BHA) etc.

1.4 Formulation by HLB:

Physically stable emulsion are achieved by presence of a condensed layer of emulgent at the oil/water interface which the interfacial and also the complex interfacial films formed by a mix of an oil soluble emulsifying agent with a water soluble one produces the foremost satisfactory emulsions. By hydrophilic- lipophilic balance (HLB) method, relative quantities of emulgent necessary to provide the foremost physically stable emulsion for a selected oil/water combination. Each surfactant is allocated an HLB numeral representing the relative quantities of the lipophilic and hydrophilic portions of the molecule. Each variety of oil used would force an emulgent of a specific HLB number so as to make sure a stable product e.g. o/w emulsion the more polar the oil phase the more polar must be the emulgent system.

1.5 Stability of Emulsion:

A stable emulsion is characterized by the absence of the inner phase, absence of creaming, absence of determination by micro-organisms and maintenance of chic in respect of appearance, color, odor, and consistency.

1.6 Nanoemulsion

Nanoemulsions are novel drug delivery system consisting of emulsified oil and water systems with mean droplet diameters starting from 50 to 1000 nm. Usually the typical droplet size is between 100 and 500 nm and might exist as oil-in-water (o/w) or water- in-oil(w/o) form, where the core particle is either oil or water, Tiny droplets of oil dispersed in water by the action of surfactant and cosurfactant are called oil-in-water (o/w)/direct/ water based nanoemulsions. Nanoemulsions are isotropic,clear kinetically stable emulsions with droplet size less than 300 nm. Nanoemulsions even have attracted an excellent attention in delivery of therapeutically active agents since approximately 40% of latest chemical entities are hydrophobic in nature and also the delivery of those poorly water soluble drugs may be a challenge for delivery of medication. In pharmaceutical field, nanoemulsions are used as a drug delivery system through various systemic routes i.e oral, topical and parenteral. The emulsion and nanoemulsion differ mainly in size and shape of the particle dispersed within the continuous phase.

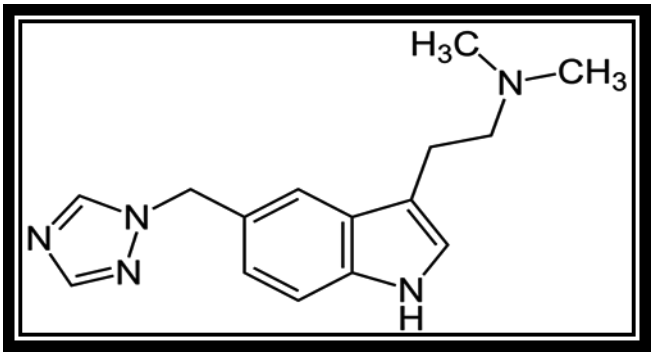
1.6.1 Types of Nanoemulsion

Depending on its composition there are three types of nanoemulsions:

a) o/w (oil in water)
b) w/o (water in oil)
c) multiple emulsion o/w/o (oil in water and aqueous phase)
d) w/o/w (water in oil in water)

2. Drug Profile

2.1 Rizatriptan Benzoate –



2.1.1 Description -

- **IUPAC Name:** N, N – Dimethyl -2 – [5 – (1, 2, 4 – triazol – 1 – methyl) – 1H – indol – 3 – yl] ethyl amine benzoate.

- **Molecular formula:** C22 H22 N5 O2
- **Molecular weight:** 391.5g/mol
- **Appearance:** White to off white powder
- **Melting point:** 178 – 180^{0}c
- **Solubility:** Readily soluble in water, soluble in methanol
- **Therapeutic category:** Antimigraine
- **Dose:** 5mg or 10mg

2.1.2 Pharmacokinetic Properties-

- **Protein binding:** 14%
- **Half- life:** 2 to 3 hrs.
- **Log P value:** 1.67
- **BCS class:** 3
- **Bioavailability:** 45%
- **Route of elimination:** 82% Urine, 12% Faces

3. METHOD OF PREPARATION

a. High pressure homogenization:
This method is widely used for the producing nanoemulsions utilizing several forces such as hydraulic shear, intense turbulence and cavitation. In this method, piston or high pressure homogeniser is used and two liquids along with surfactants, cosurfactants are made to pass through a small orifice at high pressure (500-5000 psi) to produce nanoemulsions. At first, emulsion is formed by large bulk portion of dispersed phase, which may be dilute later on. The problem of coalescence can be reduced by adding surfactants in excess amount. High pressure homogenization is a highly efficient method, available at both laboratory and large scale but consumes a large amount of energy and temperature usually increases during processing which might deteriorate the components.

b. Microfluidisation:
This mixing technique makes use of high pressure displacement pump (500–20000 psi) to produce fine nanoemulsions. Liquids (oil and water) from two opposite microchannels are made to collide with each other at a common impingement area at high pressure to create tremendous shear. Coarse emulsion is made to pass repeatedly through the interaction chamber microfluidiser till desired size of droplets is obtained.

c. Sonication:
This method can be used to produce kinetically stable nanoemulsions. Probe sonicator is brought in contact with dispersion of liquids with surfactants, cosurfactants to generate mechanical vibration and cavitation, which provides the necessary energy input for formation of small sized droplets. Sonication can be widely used to preparenanoemulsions on small scale however care must be taken to prevent shear induced coalescence.

d. Phase inversion temperature technique:
Phase transition is brought about either by alteration in temperature at constant composition or keeping the temperature constant and altering the composition. In this technique a mixture of oil, water and nonionic surfactants at room temperature exhibiting a positive curvature are taken on increasing the temperature; the polyethoxylated surfactant becomes lipophilic (due to dehydration) and gets solubilized in the oily phase. This results in the phase inversion and o/w emulsion changes to w/o emulsion exhibiting a negative curvature. It must be noted here that at intermediate temperature (HLB temperature) highly unstable emulsions are formed as the curvature approaches zero. A quick change in temperature prevents coalescence and produce stable nanoemulsions.

4. NANOEMULSION AS TOPICAL DRUG DELIVERY SYSTEM

Nanoemulsion in Topical Application Nanoemulsion could be a promising alternative to extend drug delivery system penetration and targeting poorly soluble drugs, by increasing its absorption through the skin, better retention time of drug within the place and eventually lead to fewer side effects. The advantages of nanoemulsion with globules in nano-scale size of an emulsion don't rely on the emulsion physical properties itself, besides that; nanoemulsion improves the permeation of drug through skin. Additionally, the tiny size of particles, the more amount of drug is in a position to be incorporated within the formulation, which subsequently increases the thermodynamics towards the skin. The best obstacle upon transdermal drug delivery refers to barrier properties of horny layer a ten µm to twenty µm thick tissue layers with great composed structured lipid/protein matrix.

4.1 Advantages of Nanoemulsion

a) Nanoemulsions are thermodynamically and kinetically stable therefore flocculation, creaming and coalescence do not occur.
b) It is non -toxic and non-irritant.
c) Nanoemulsion is administered by various routes, such as oral, topical, parental and transdermal etc.
d) Nanoemulsions can deliver both hydrophilic and lipophilic drugs.

4.2. Limitations of Nanoemulsion

a. Requires use of high energy devices such as high pressure homogenisers and ultrasonic that leads to increase in cost.
b. Poor solubilizing capacity for substances with high melting point.
c. Lack of in depth knowledge on mechanism of Ostwald ripening and its reduction.
d. Stability of nanoemulsions might be affected by temperature and pH variation.

4.3. Application of Nanoemulsion:

a. Parentral Nanoemulsion
b. Oral drug delivery
c. Topical drug delivery
d. Ocular and Pulmonary drug delivery
e. Intranasal drug delivery

4.4. Components of Nanoemulsion

The main components of nanoemulsion are as follows:

a. Oil:
Oils could also be wont to solubilize the lipophilic drugs and increase the drug transport through intestinal vascular system. Select of oil component can modulate the topical drug delivery from O/W and W/O nanoemulsions. Long and medium chain triglycerides oils with different degree of saturation are used as oil phase, although the latter are preferred and are safe. a mix of oils and triglycerides is also accustomed emulsify the drug. Semisynthetic medium chain derivatives possessing surfactant like properties are used now-a-days as oily phase. Commonly used oils in formulating nanoemulsions are: oil, ethyl oleate, sesame oil, castor oil, arachis oil, corn oil, lanolin, jojoba oil, Capryo l90, triactin, isopropyl myristate, olive oil, oleic acid, isopropyl palmitate, Labrafil MM44CS,palm oil esters, corn oil, Labrafac Lipophile WL1349, Maisine 35-1, Captex 200, Captex 355, captex8000, Miglyol 812, Sefsol 218, Witepsol, Myritol 318 and Capmul MCM.

b. Surfactants (surface active agents):
Surfactant molecules carries with it two parts, polar and nonpolar region. They're classified in keeping with the character of polar group within the molecule into: anionic, cationic, nonionic & zwitterionic surfactants. Surfactants contribute significantly within the formulation of nanoemulsions by lowering the interfacial surface tension between two immiscible liquids and make them miscible. They decrease the strain required to interrupt the visit lowering the Laplace pressure. Further, they prevent coalescence of newly formed drops. Hydrophile–lipophile balance (HLB) and important packing parameter (CPP) must be taken under consideration for surfactant selection. Surfactants with high HLB (8–18) are wont to prepare o/w nanoemulsions (Table 2).

Sr. No.	Surfactant
1	Labrasol
2	Cremophor RH 40, EL
3	Span 20
4	Tagat TO
5	Tween 20,80
6	PEG 400
7	Brij 30
8	Emulphor-620

Table 2: Surfactants used in preparing o/w Nano emulsions

c. Cosurfactants:
A single chain surfactant alone might not be able to reduce the oil/water surface tension sufficiently for preparing nanoemulsions, hence arises the requirement of cosurfactants (Table 3). These are ampiphilic in nature with a bent to partition in large amounts at the surfactant interfacial monolayer. They reduce interfacial surface tension by increasing the fluidity of the interface and entropy of the system. HLB of the system will be modified by proper selection of surfactants and cosurfactants.

Sr. No.	Cosurfactant
1	Propylene glycol, glycerine
2	Polyethylene glycol
3	Lecithin
4	Plurol Oleique CC497
5	Transcutol P Transcutol HP
6	Ethanol
7	Propanolol
8	Butanol
9	Carbitol

Table 3: Cosurfactants used in formulating Nano emulsion

d. Additives:

Additives are added to make the nanoemulsions last for longer periods. (Table 4)

Sr. No.	Additives	Commonly used additives
1	Antioxidant	Ascorbic acid, tocoferol
2	Tonicity modifiers	Glycerol
3	pH adjusting agents	Solution of sodium hydroxide and hydrochloric acid
4	Stabilizers	Oleic acid, cholic acid
5	Preservatives	Methyl paraben, Propyl paraben

Table 4: Additives used in formulating Nanoemulsion

e. Aqueous phase:
The size of the droplets and stability of nanoemulsion may be affected by the nature of the aqueous phase. Careful consideration should be given to pH and presence of electrolytes in aqueous phase during nanoemulsion preparation.

4.5 Instability In Nanoemulsions

Emulsion stability is dependent on role of surfactants, its composition and the drop size distribution. Nanoemulsions exhibit stability against sedimentation or creaming Due to the small size of droplets. Diffusion rate and Brownian motion exhibited by these droplets predominates over sedimentation/creaming rate due to gravity. Flocculation does not occur in nanoemulsions prepared by using nonionic surfactants as no attractive forces are created. Nanoemeulsions may remain stable for a short span to years depending on how they are formulated and other process parameters involved in formation. They are sometimes referred to as "approaching thermodynamic stability". The solubility of phases in each other, type and amount of surfactant used, nature of the interfacial layer formed governs that how stable an emulsion would be. Instability (irreversible in nature) in nanoemulsions occurs due to alteration in size through mechanisms such as Coalescence and Ostwald ripening.

a. Coalescence:
Coalescence is a phenomenon resulting from fusion of two or more droplets into one larger drop. It happens when the force of adhesion between two droplets exceeds the turbulent force creating dispersion, resulting in the breakdown of the thin film existing between adjacent droplets and resultant in blend of these lesser droplets to become a bigger sized drop. It can be prevented by addition of surfactants having same charges on them which would cause repulsion between two droplets. As the time passes, coalescence in the drops can follow varied behavior. It may show homogenous growth where average size of the droplet increases with time or more often results in early phase separation (heterogeneous growth).

b. Ostwald ripening:
Ostwald ripening in nanoemulsions is characterized by change in droplet size with the passage of time due to molecular diffusion. The process of mass transfer occurs when droplets form dispersed phase (region with high Laplace pressure) migrate to continuous phase (region with low Laplace pressure).When nanoemulsions are stored for a long period of time, there is change in droplet size distribution towards larger sized drops and turbidity appears in nanoemulsions. Ostwald ripening further possess a problem in formulation delivery.

5. GEL

Gels are the semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle

rendered jelly like by the addition of a gelling agent. They have one characteristics feature that is the presence of a continuous structure providing solid like properties. In polar gel, natural or synthetic polymer builds a three dimensional matrix throughout the hydrophilic liquid. The appearance of gels formulation is opaque due to the presence of colloidal substance and liquid.

5.1 Classification of Gel

Class	Examples
Inorganic	Aluminium hydroxide gel, Bentonite magma
Organic	Carbopol, Tragacanth
Hydrogels	Methyl cellulose, Sodium carboxymethyl cellulose, Pectin paste, Silica, Pluronic Bentonite gel
Organogels	Petroleum, Carbowax bases, Mineral oil

Table 5: General classification of Gels

5.2 Characteristics of Gels

a. Swelling

Gels can swell, absorbing liquid with a rise in volume. this will be looked on because the initial phase of dissolution. Solvent penetrates the gel matrix in order that gel-gel interactions are replaced by gel-solvent interactions. Limited swelling is typically the results of some extent of cross-linking within the gel matrix that stops total dissolution. Such gel swells considerably when the solvent mixture possesses a solubility parameter equivalent to that of the gellant.

b. Syneresis

Many gel systems undergo contraction upon standing. The interstitial fluid is expressed, collecting at the exterior of the gel. This process, cited as syneresis, isn't limited to organic hydrogels, but has been seen in organogels and inorganic hydrogels similarly. Typically, syneresis becomes more pronounced because the concentration of polymer decreases.

c. Ageing

Colloidal systems usually exhibit slow spontaneous aggregation. This process is brought up as ageing. In gels, ageing ends up in the gradual formation of a dense network of the gelling agent. The immer suggests that this process is analogous to the first gelling process and continues after the initial gelation, since the fluid medium is lost from the newly formed gel.

d. Structure

The stiffness of a gel arises from the presence of a link formed by the interlinking of particles of the gelling agents. The character of the particle and therefore the style of force that's chargeable for the linkages determine the structure of the network and therefore the properties of the gel. A gel is classified supported colloidal phases, nature of solvent used, physical nature and rheological properties, etc. Solutions of the gelling agents and spreading of flocculated solid are pseudo plastic i.e., exhibiting Non- Newtonian flow performance.

e. Rheology

Solutions of the gelling agents and dispersion of flocculated solid are pseudo plasti i.e., exhibiting Non-Newtonian flow behavior, characterized by a decrease in viscosity with a rise in shear rate. The tenuous structure of inorganic particles dispersed in water is disrupted by applied shear stress because of breaking down of inter particulate association, exhibiting a greater tendency to flow. Similarly, for macromolecules the applied shear stress aligns the molecules within the direction of stress, straightening them out and lessening the resistance to flow. Suppository bases.

5.3. Uses of Gels

a) As delivery systems for orally administered drugs.
b) For topical drugs applied directly to the skin, mucous membrane or the eye.
c) As long acting forms of drug injected intramuscularly or implanted into the body.
d) As binders in tablet granulation, protective colloids in suspensions, thickeners in oral liquid and suppository bases.

6. NANOEMULGEL

Formation containing Nanoemulsion in gel base are called nanoemulgel, is that the addition of Nanoemulsion system intergraded into gel matrix which influences a better skin permeation. This mixture of

nanomulgel acts as drug reservoirs, influencing the discharge of drug from inner phase to outer phase and further. Nanoemulgel on intact with skin release the oil droplets from the gel and this oil droplets penetrate into the SC of the skin and deliver the drug to intended site. Nanoemulsion-gel have an honest adhesion property and high solubilising of drug in oil phase ends up in larger concentration gradient towards the skin that further increase skin penetration of drug. Also patient compliance is improved thanks to increased spared ability compare to creams and ointments and decreased stickiness.

6.1 Advantage of Nanoemulgel:

a. Stability of Nanoemulsion is enhanced because of distribution of oil droplets in Gel base; where affinity of the drug toward oil determines stability.
b. Also good adhesion on the skin with high solubilising power ends up in high concentration gradient that increases penetration of drug because it moves down.
c. Moreover, these forms of formulation give support to delivery of lipophilic and poorly water soluble drugs and also improve patient compliance.
d. Nanoemulgel also helps in controlled release of medicine having the shorter half-life.
e. Provide higher Spread-ability of the formulation than creams.

6.2 Methods of Formulation:

Formulation of Nanoemulsion-gel is summarized in to following steps,

a. Screening of components
b. Preparation of Nanoemulsion
c. Preparation of Nanoemulgel.

a. Screening of components:

Drug Solubility made up our minds in several oils by excess addition of drug into different components followed by continuously stirred 72 hours to realize equilibrium. Afterward samples centrifuged and supernatant was taken and solubility was resolute by appropriate analytical methods. Then, excipients in each category with the best solubility of drug are selected for further studies,

i. Psedoternary phase diagram:

Surfactant and cosurfactant (Nmix) were mixed in numerous ratios (2:1, 3:1 and 5:1). Each ratio chosen in increasing amount of surfactant regard to co surfactant for a study on the phase diagrams. Now aqueous phase (Distilled water) used as dilution media. Oil and Nmix was mixed at different ratios from 9:1 to 1:9 in numerous vials for every Nmix. Main objective for this can be to hide for the study to come to a decision boundaries of phases formed within the diagrams. it had been developed using titration method with help of water as aqueous media. Gentle titration of oil and mix is accomplished and visual observations are ready for transparency of Nanoemulsion. The state of Nanoemulsion is marked on one axis of aqueous phase, the other of oil and also the third one amongst Nmix (surfactant and co-surfactant).

b. Preparation of Nanoemulsion:

The drug is then solubilized in oil and oil is addend into mix, this mixture is diluted with water to create of Nanoemulsion of given drug.

c. Preparation of Nanoemulgel:

Gel base is ready using 1g of the Carbopol during a required quantity of water. Later complete swelling and spreading of Carbopol solution during 24 hours period, set Nanoemulsion is slowly added under continues stirring. Addition of Triethanolamine gives homogeneous gel dispersion. Finally required remaining part is adjusted with H2O Figure 3

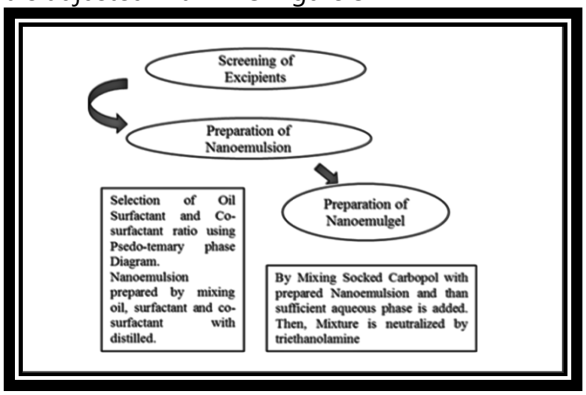


Fig. 03: Flowchart for Preparation of Nanoemulgel

6.3 Optimization and Evaluation

a. Measurement of pH:

Numerous Topical preparations have pH in range of 5-6 measured by using pH meter. For testing, 1g of gel is dissolve in 10ml water. PH of every formulation is completed on triplicate to avoid error.

b. Size of globules:

To determine this parameter 1.0 gm of gel was dissolved in water and stirred to urge dispersion so sample was injected into the photocell of Malvern zetasizerr.

c. Swelling Index:

1 gm. of prepared topical nanoemulgel is taken on porous foil which is then placed on 10 ml of 0.1 N NaOH solutions. Sample removed time to time and weight is noted till no further change in weight:

Swelling Index (SW) % = [[Wt-Wo]/Wo]*100

Where, (SW) % = Percentage swelling,

Wo = Original weight of nanoemulgel

Wt. = Weight of swollen nanoemulgel at time t

d. Measurement of Bio adhesive strength

1 glass slide separated from 2 other glassed plates on each arm of apparatus. Single plate is for adding weight. Correctly 1 gm. of nanoemulgel is placed between slides containing rate skin pieces (hairless). Putting weight on single glass slide create some pressure to removed sandwich of 2 slides. Addition of extra weight is followed as 200 mg/ min to until the detachment of the skin surface. Required weight to detach the nanoemulgel from skin gave bio adhesive strength1. It is calculated by using following equation: Bio adhesive Strength = W / A

Where, W= Weight required (in gms) and A=Area (cm^2)

e. Determination of Rheological properties

20gm of Nanoemulsion-gel filled in 25ml beaker was accustomed measure viscosity by using Spindle number S64 by Brookfield viscometer

f. Determination of % drug content: 1 g of Nanoemulgel is mixed with 25 ml of methanol. This solution is sonicated for 30 min. Drug content was calculated using the appropriate analytical method from this solution.

g. Spreadability of Gellifed Nanoemulgel:

It is measured by using Slip and Drag basis, as suggested by Mutimer, Here 2gm add Nanoemulgel is palced on lower ground slide which is fixed with wooden block and sandwiched is ready by other glass slide having similar size which is attached with hook having 500mg weight placed. After five min extra weight was retained on pan connected with second slide. Time to hide 5cm distance for upper slide was noted and wont to calculate spreadability by using following equation: Spreadability (S) = M*L / T

Where, M = Weight tied to upper slide, L = Length of glass slides. T = Time taken to cover distance by upper slide

h. Skin irritation test

0.25 gm Nanoemulgel is applied to every different site (two sites/rabbit). After 24 hr of application rabbit skin site are wiped and cleaned, Change in colour of skin or undesirable change in morphology is noted and checked.

i. In-vitro Diffusion studies

Franz diffusion cell is employed to perform diffusion study of prepared nanomeulgel. A cellophane membrane is employed for study and 0.5g of sample applied on membrane and diffusion is meted out for 8 hr at 37±1°C using phosphate buffer (pH 7.4). At quantity of 1 hr, 1 ml pg sample is collected and replaced with new solution. Collected samples are examined by using appropriate analytical method.

7. MECHANISM

There are different numbers of components, for example,

1. PH responsive system.

2. Thermosensitive and volume progress component.

3. Photoisomerisation.

7.1 pH Responsive Mechanism:

As the name shows, sedate discharge reacts to the pH changes within the encompassing natural condition. At the top of the day, the medication arrival of can happen in physiological situations that specific take pH esteems. the foremost discharge will occur in proper pH which means that the discharge is predominantly accomplished in an exceedingly focused on zone of the body that has that pH. this technique can keen about the way that polymers utilized within the combination of a nanogel contain pH bunches that deionized within the polymeric system. The outcomes in increment in pressure, the growing and porosity of the polymer which cause the arrival of the bound atoms.

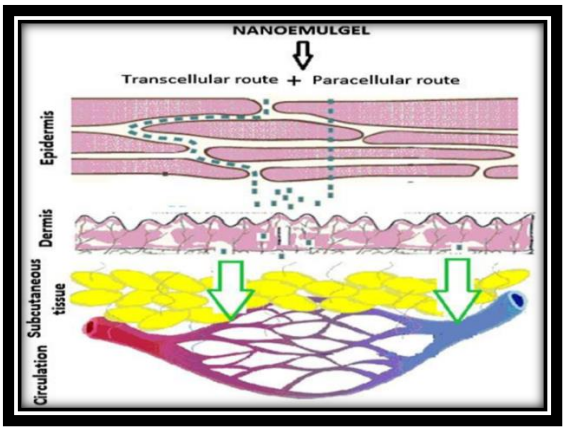


Fig. 4 Mechanism of Nanoemulgel.

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