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TOPICAL GEL: A NOVEL APPROACH FOR DEVELOPMENT OF TOPICAL DRUG DELIVERY SYSTEM

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Abstract

Topical gel are transparent or translucent semisolid formulation and used for the localized drug delivery anywhere in the body through rectal, vaginal, ophthalmic and skin as topical route. Topical gel formulation provides a suitable delivery system for drugs because they are less greasy and can be easily remove from skin. Gel formulation provided better application property and stability in comparison to ointments and cream. Different methods are used to enhancement of permeability and bioavailability of topical gels that can be incorporate into a novel drug delivery system like emulgel, solid dispersion into gel, hydrogel, microemulsion gel, solid lipid nanoparticles into gel, liposomal gel. This review is concern with all detail information regarding novel approach to topical gel formulations, advantages and disadvantages of topical gel, classification of gel, basic components of topical drug delivery systems, and evaluation of gel and mainly highlights the novel approach of gel formulation.

Keywords: Topical gel, skin, Novel Drug Delivery system. Topical drug delivery.

Introduction

Topical gels are transparent or translucent semisolid formulations containing a high ratio of solvent/gelling agent. Gels defined as semirigid system in which the movement of the dispersing medium is restricted by interlacing three-dimensional networks of particles or solvated macromolecules of the dispersed phase. A high degree of physical or chemical cross-linking may be involved. The U.S.P. defines gels as a semisolid system consisting of dispersion made up of either small inorganic particle or large organic molecule enclosing and interpenetrated by liquid. The inorganic

particles form a three dimensional 'house of cards' structure. Gel consist of two phase system in which organic particles are not dissolved but merely dispersed throughout the continuous phase and large organic particles are dissolved into continuous phase, randomly coiled in the flexible chains. Gels have viscoelastic property. The solid like matrix structure formed during storage breaks easily on a shaking a bottle or squeezing a tube. Thinning under pressure allows it easily applicable on skin and it's solid like matrix makes it adhere onto the skin when application is over.[1-3]Topical drug administration is localized drug delivery system anywhere in the body through rectal, ophthalmic, vaginal and skin as topical route. Most topical gels are prepared with organic polymers, such as carbomers, that impart an aesthetically pleasing, clear, sparkling appearance to the products and are easily washed off from the skin with water. Use of type of bases in formulating a topical dermatological product greatly influences its effectiveness. Bases containing large amounts of oleaginous substances which provide an emollient effect to dry irritated skin. An occlusive barrier on the skin can form by non-volatile oleaginous substances (e.g. hydrocarbon bases) that prevent escape of moisture from the skin into the environment.[2]

Advantages of topical gel [4]

- They can avoid gastrointestinal drug absorption difficulties caused by gastrointestinal p^H and enzymatic activity and drug interaction with food and drinks
- To avoid the first pass effect that is the initial pass of the drug substance through the systemic and partial circulation following gastrointestinal absorption, avoiding the deactivation by digestive and liver enzymes
- They are less greasy in nature and can be easily removed from the skin.
- Cost effective
- Reduction of dose as compare to the oral dosage form
- Localized effect with the minimum side effects

Disadvantages-

- Poor permeability of some drugs through the skin
- Possibility of allergenic reactions
- Can be used only for drugs which require very small plasma concentration for action

- Enzyme in epidermis may denature the drugs
- Larger particle size drugs not easy to absorb through the skin

Classification of gel [5]

Gels can be classified based on the basis of colloidal phases, nature of solvent used, physical nature and rheological properties.

A. Based on colloidal system

- Two phase system(Inorganic)- If the particle size of dispersed phase is relatively large and form the three dimensional structure throughout gel such as a system consist of floccules of small particle rather than layer molecule and gel structure in this system is not always stable. E.g.Aluminum Hydroxide Gel USP
- Single phase system (Organic) - These consist of large organic molecule existing on the twisted stands dissolved in continuous phase.

B. Based on nature of solvent used

- Hydrogel –Here they contain water as their continuous liquid phase

  E.g. Gelatin, cellulose derivatives and poloxamer gel
- Organic gel (with a non-aqueous solvent) - These contain a non –aqueous solvent as continuous phase.
- Xerogels - Xerogels are solid gel with low solvent concentration and produced by evaporation of solvent or freeze drying.E.g. Dry cellulose and polystyrene.

3. Based on rheological properties

Usually gels exhibit non-Newtonian flow properties. They are classified into,

- Plastic gels
- Pseudo plastic gels
- Thixotropic gels

4. Based on physical nature

- Rigid gels
- Elastic gels

Ideal properties of topical gel [3]

- Should be inert, compatible with other additives
- Should be non-toxic
- Should be stable at storage condition
- Should be free from microbial contamination
- Should be maintain all rheological properties of gel
- Should be economical
- Should be washable with water and free from staining nature
- Should be convenient in handling and its application
- Should be passes properties such as thixotropic, greaseless and emollient

Basic components of Topical gel [3, 6]

A) Drug substances-. Mainly NSAID'S agent, antifungal agent, antibacterial agent etc. used. Judicious choice of the drug plays an important role in the successful development of a topical product. The important drug properties that effect its diffusion through the device as well as through skin are as follows,

a. Physicochemical properties:

- Less than 500 Daltons molecular weight of drug should be required
- Adequate lipophilicity of drug must be required
- A pH of aqueous solution (saturated) of drug should be required value between 5 and 9.
- Drugs which are highly acidic or alkaline in solution are not suitable candidates for topical delivery.

b. Biological properties*:*

- The drug should not be directly irritated to the skin
- The drug should not stimulate an immune reaction in the skin
- Drugs, which degrade in gastrointestinal tract or are inactivated by hepatic first pass effect, aresuitable for topical delivery
- Tolerance to the drug must not develop under the near zero order release profile of topical delivery

- Drugs which have to be administered for a long time or which cause adverse effects to non-targeted tissue can also be formulated for topical delivery

B) Polymers- Mechanism of drug release depends upon the physicochemical properties of drug and polymer used. Polymers are used to give the structural network, which is essential for preparation of gel. Gel forming polymers are as follow:

Table 1Examples of polymers

Natural Polymers	Semisynthetic Polymers	Synthetic Polymers
Gelatin	Carboxy methyl cellulose	Carbopol-940
Tragacanth	HPMC	Poloxamer
Guar gum	Hydroxy ethyl cellulose	Poly vinyl alcohol
Xanthin	Hydroxymethyl cellulose	Polyethylene
Agar	Methyl cellulose	Polyacrylamide

C) Penetration enhancers Promote skin permeability by altering the skin as a barrier to the flux of desired penetrant and are considered as integral part of most topical formulation. Ideally, penetration enhancers reversibly reduce the barrier resistance of the stratum corneum without damaging viable cells. Examples-Water, Essential oils, urea and its derivatives

Ideal properties of penetration enhancers [9, 10]

- They should be non-toxic, non-irritating and non-allergenic
- They would ideally work rapidly; the activity and duration of effect should be both predictable and reproducible
- They should have no pharmacological activity within the body
- The penetration enhancers should work unidirectional, i.e., they should allow therapeutic agents into the body whilst preventing the loss of endogenous materials from the body
- When removed from the skin, barrier properties should return both rapidly and fully to normal
- They should be cosmetically acceptable with an appropriate skin feel

D) Preservatives- Used to resist microbial attack. Examples- Methyl paraben, Propyl paraben

E) Surfactants- Reduces interfacial tension. Example- sodium lauryl sulphate, sodium glycolate

F) Chelating agent- Bases and medicaments in gels are sensitive to heavy metals, hence added to protect. Example- E.D.T.A., methylated cyclodextrin

Methods of preparation of gel [7]

- COLD METHOD- In this method the entire ingredient mixed together to form a homogenous mass, under low temperature at about 5^0C. In this polymer and penetration enhancer are mixed together to form a solution A, then drug and solvent mixed to form solution B. After that with constant stirring poured solution B into solution A.
- DISPERSION METHOD- In this method polymer is dispersed over water for 2 hrs till all the polymer is soaked with water, then addition of remaining ingredients is done with stirring until a homogenous mass is formed.
- CHEMICAL REACTION-In this method gel formed by precipretation. Silica gel and aluminium hydroxide gel are the examples. Silica gel is produced by interaction of sodium silicate and acids in aqueous solution.
- TEMPERATURE EFFECT- With decreased in temperature, solubility of most lipophilic colloid e.g. gelatin, agar is reduced. So that when cool concentrated hot sol gel are produced.
- FLOCCULATION–In this method gelatin is produced by adding just sufficient quantity of salt to precipitate to produce age state but insufficient to bring about complete precipretation.

NOVEL APPROACHES FOR GEL FORMULATION-

A) Hydrogel-

Hydrogels are hydrophilic polymeric network of three dimensional cross linked structures that absorb substantial amount of water. Cross linking facilitates insolubility in water because of ionic interaction and hydrogen bonding. It also provides required mechanical strength and physical integrity to the Hydrogels. Thus, hydrogels can imbibe water nearly 10-20 times its molecular weight and hence become swollen. Some examples of Hydrogels include contact lenses, wound dressing, superabsorbents. [8]

Advantages

- Biocompatible
- Easy to modify
- Entrapment of microbial cells within polyurethane hydrogel beads lead to low toxicity

- Environmentally sensitive hydrogels have the ability to sense changes of pH, temperature or the concentration of metabolite and release their load as result of such a change.
- Natural hydrogel materials are being investigated for tissue engineering, which include agarose, methylcellulose and other naturally derived polymers

Methods of preparation of hydrogels [8]

1. Use of crosslinkers
2. Isostatic ultra high pressure (IUHP)
3. Use of nucleophilic substitution reaction
4. Use of gelling agent
5. Use of irradiation and freeze thawing
6. Synthesis of hydrogel in industry

Table 2 Reported examples of hydrogel [9-11]

Drug	Category	Gelling agent	Reference
Nicotine	Stimulants	Agar	Conghey et.al.(1998)
Prazocine HCL	Antihypertensive	Sodium alginate	Raghvendra et.al.(2010)
Rutin	Antioxidant	Carbopol, Acacia, HPMC	Soni et.al.(2012)

B) Microemulsion

Microemulsion are isotropic and thermodynamically stable multicomponent fluids composed of water, oil, surfactants and / cosurfactants whose diameter is in the range of 10-140 nm. Drug transport from microemulsion is recorded better than that from other ointment. One important consequence is that the stability of the microemulsion based gels (MBGs) is much better compared to that of conventional hydrogels. One other reason for this is that the MBGs are prepared from w/o microemulsion which is thermodynamically stable systems and the organic solvent as external phase which could offer superior resistance to microbial contamination compared to aqueous phase. Moreover, due to the increasing of viscosity of the system by incorporating gelatin into W/O microemulsion, the MBGs are suitable to be used as a kind of sustained release drug delivery systems. Other properties that make the MBGs attractive as drug delivery vehicles include their electrical conductivity to be applied in iontophoretic drug delivery systems. [12-13]

Advantages [14]

- Increased rate of absorption
- Eliminate variability in absorption
- Helps solubilize lipophilic drug
- Increased bioavailability
- Penetration of the drug moiety is rapid and efficient
- Less amount of energy required

Methods of preparation

1. Phase inversion method

2. Phase titration method

Evaluation of Microemulsion-

Following are different parameters are evaluated for microemulsion,

1. Phase behavior study

2. Viscosity measurement

3. Isotropic nature

Table 3Reported examples of microemulsion based gel [15-18]

Drug	Category	Gelling agent	Reference
Tretioin	Vitamin A	Carbomer 934	Suthar et.al.(2009)
Ibuprofen	NSAID	Xanthan gum	Chen et.al (2006)
Bifanazole	Antifungal	HPMC	Sabale&Vora(2012)
Itraconazole	Antifungal	Xanthangum,Carbopol 940	Lee et.al.(2010)

C) **Solid Lipid Nanoparticles-**

Nanoparticles are the colloidal particles having range size between 10 and 1000 nm. Synthetic/natural polymers are used for manufacturing nanoparticles and ideally suited to optimize drug delivery and reduce toxicity. Over the years, they have emerged as a variable substitute to liposomes as drug carriers. The successful implementation of nanoparticles for drug delivery depends on their ability to penetrate through several anatomical barriers, sustained release of their contents and their stability in the nanometer size. To overcome these limitations of polymeric

nanoparticles, lipids have been put forward as an alternative carrier, particularly for lipophilic pharmaceuticals. These lipid nanoparticles are known as solid lipid nanoparticles (SLNs), which are attracting wide attention of formulators world-wide. [19]

Advantages of SLNs [20]

- Shows improved and better bioavailability of poorly water soluble molecules
- Site specific delivery of drugs, enhanced drug penetration into the skin via dermal application
- Possibility of scaling up.
- Protection of chemically labile agents from degradation in the gut and sensitive molecules from outer environment
- They have better stability than liposomes
- Enhance the bioavailability of entrapped bioactive and chemical production of labile incorporated compound.
- High concentration of functional compound achieved.

Methods of preparation for SLNs [21]

1. Homogenization Method

A) Hot homogenization

B) Cold Homogenization

2. Solvent evaporation method

3. Solvent emulsification-diffusion method

4. Microemulsion based method

5. Supercritical fluid method

6. Spray drying method

7. Double emulsion method

8. Precipitation technique

9. Film-ultrasound dispersion

10. High-speed homogenization followed by ultra-sonication method

Evaluation of SLNs-

SLNs are evaluated for following Parameters,

1. Particle size and zeta potential- Photon electron microscopy, Atomic force microscopy

2. Surface charge -Acoustic method

3. Diffusion -Franz diffusion cell

4. Physical characterization - Scanning electron microscope, Transmission electron microscope

Table 4 Reported examples of SLNs based gel [22-25]

Drug	Category	Gelling agent	Reference
Miconazole nitrate	Antifungal	Carbopol 934P	Sanap&Mohanta(2013)
Imiquimod	-	Carbopol 934	Patel et.al. (2013)
Aceclofenac	Anti-inflammatory	Carbopol 940P,Xanthan gum, Chitoson, HPMC	Patel et.al.(2012)
Diclofenac sodium	Anti-inflammatory	Carbopol 934	Gaddam& Aukunuru (2010)

D) Liposomes

Liposomes established themselves as a promising novel drug delivery vehicle in several different basic sciences and as a viable alternative in several applications. Liposomes are microscopic spheres with an aqueous core surrounded by one or more outer shells consisting of lipids arranged in a bilayer configuration. Liposomes are having ability to encapsulate hydrophilic and lipophilic drugs and protect them from degradation. Liposome gives better absorption because it has affinity to keratin of horny layer of skin and can penetrate deeper into skin. When applied on the skin, liposomes may act as a solubilizing matrix for poorly soluble drugs, penetration enhancer as well as local depot at the same time diminishing the side effects of these drugs. Topical liposome formulations could be less toxic and more effective than conventional formulations. The liposome gel formulations could perform therapeutically better effects as compared to the conventional formulations, as prolonged and controlled release topical dosage forms, which may lead to improved efficiency and better patient compliance.[26-27]

Advantages [27]

- Precipitation at the injection site and in the blood circulation can be prevented.

- Phospholipids are one of the few solubilizers that are well tolerated intravenously.
- Increase safety and therapeutic index.
- Increase stability via encapsulation
- Site avoidance effect.
- Reduces toxicity of the encapsulated agents

Drug criteria for topical liposomal drug delivery system

- There are drugs which are known to have severe side effects by the conventional way of topical administration, e.g. topical glucocorticosteroids.
- There are substances which normally are not effective by topical application E.g. interferon.
- There are drugs which only show insufficient effects when applied topically. E.g. Hamamelis distillate.
- Drugs that on conventional topical application show local irritant effect and flare up reactions at thebeginning of treatment, e.g. Retinoid (Tretinoin).
- Drugs which require prolonged application time and high drug concentrations to alleviate unpleasant sensations often associated with dermatological diseases or their treatment e.g. Local anaesthetics (Tetracaine).

Methods of preparation of gel

1. Mechanical dispersion method
2. Solvent dispersion method
3. Detergent removal method

Characterisation of liposomes [26-27]

1. Biological characterization- Sterility, Pyrogenisity, Animal toxicity

2. Chemical characterization- Phospholipid concentration, Cholesterol concentration, Drug concentration, Phospholipid hydrolysis and oxidation, pH

3. Physical characterization- Surface morphology, Vesicle size, Size distribution, Surface charge, Lamellarity, Drug release, Percent capture, Phase behavior

Table 5 Reported examples of liposome gel [28-31]

DRUG	Category	Gelling agent	References
Fluconazole	Antifungal	Carbopol 934NF	Mitkari et.al (2010)
Ketoconazole	Antifungals	Carbopol	Rakesh et. Al.(2009)
Selegiline	Monoamine oxidase inhibitor	Carbopol	Megha et.al.(2012)
Ketoprofen	NSAID	Carbopol 934	Mansoori et.al (2012)

E) Emulgel

Emulgels are combination of gels and emulsions .Major limitation of gel is found in the delivery of hydrophobic drugs. So that to overcome this limitation an emulsion based approach is being used. Polymer can act as emulsifiers and thickeners because the gelling capacity of these compounds allows the formulation of stable emulsions and creams by decreasing surface and interfacial tension and at the same time increasing the viscosity of the aqueous phase. In fact, a gelling agent present in the water phase converts a classical emulsion into an emulgel. Both o/w and w/o emulsions are used as vehicles for the delivery of various drugs to the skin**.** Emulgels for dermatological use have several favorable properties such as being greaseless, thixotropic, easily spreadable, emollient, easilyremovable, nonstaining, long shelf life, transparent & pleasing appearance [32-33]

Advantages

- Hydrophobic drugs can be easily incorporated into gel
- Low preparation cost
- Better stability
- Controlled release:-Emulgels used to prolong drugs effect having short half life
- Self medication possible

Important Constituents of emulgel preparation [32-34]

1. Aqueous Material: This forms the aqueous phase of the emulsion.e.g. water, alcohols etc.

2. Oils: These agents form the oily phase. For externally applied emulsions, mineral oils, either alone or combined with soft or hard paraffin, are widely used both as the vehicle for the drug and for their occlusive and sensory characteristics.

3. Emulsifiers: Emulsifying agents are used both to promote emulsification at the time of manufacture and to control stability during a shelf life that can vary from days for extemporaneously prepared emulsions to months or years for commercial preparations.eg Span 80, Tween 80, Stearic acid, and Sodium stearate

4. Gelling Agent: These are the agents used to increase the consistency of any dosage form can also be used as thickening agent.e.g. Carbopol, HPMC. Gelatin

5. Permeation Enhancers: These are agents that partition into and interact with skin constituents to induce a temporary and reversible increase in skin permeability.

Table 6 Examples of emulgel [35-38]

Drug	Category	Gelling agent	Reference
MiconazoleNitrate	Antifungal	Carbopol	Jain et.al.(2011)
Ketoconazole	Antifungal	Carbopol 934 &Carbopol 940	Jain et.al.(2010)
Itraconazole	Antifungal	Carbopol 934	Deveda et.al.(2010)
Ibuprofen	NASID	Carbopol 940	Chaskar et. Al.(2011)

F) Solid Dispersion

The term solid dispersion refers to a group of solid products consisting of at least two different components, generally a hydrophilic matrix and a hydrophobic drug. The matrix can be either crystalline or amorphous. The drug can be dispersed molecularly, in amorphous particles (clusters) or in crystalline particles. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. Oral bioavailability of a drug depends on its solubility and/or dissolution rate, and dissolution may be the rate determining step for the onset of therapeutic activity, several techniques have been developed over the years to enhance the dissolution of the drug, such as inclusion complexation, salt formation, and solvent deposition. Among other techniques solid dispersion (SD), which was introduced in the early 1970s, is an effective method for increasing the dissolution rate of poorly soluble drugs, hence, improving their bioavailability. Solid dispersion is one of the approaches employed to improve dissolution of poorly soluble drugs whose absorption is dissolution rate limited.[39-41]

Advantages of Solid Dispersion [42]

1. Reduced particle size and thus improved surface area and dissolution rate. The ultimately result in improving bioavailability.

2. Wettability is improved results in increased solubility. (Carriers play the major role to improve the wettability)

3. Higher degree of porosity of particles. The increased porosity of solid dispersion particles accelerates the drug release profile. Increased porosity also depends on the carrier properties.

4. In solid dispersions drugs are presented as supersaturated solutions which are considered to be metastable polymorphic form. Thus presenting drugs in amorphous form increase the solubility of the particles.

5. Rapid dissolution rates hence an increase in the rate and extent of the absorption of the drug.

Methods of preparation of solid dispersion [43]

1. Solvent evaporation method

2. Hot melt extrusion

3. Fusion method

4. Physical mixing

5. Supercritical fluid technology

6. Kneading method

Evaluation & Characterization of Solid Dispersion [41]

1. Physical appearance

2. Percent Practical Yield

3. Drug content

4. Aqueous solubility studies

5. Dissolution Studies

6. Drug carrier compatibility

This study is done to determine the interactions if any between the drug and carrier and to determine the formation of inclusion complexes. Methods used for this purpose are:

(a) Fourier Transform Infra-Red (FTIR) Spectroscopy

(b) Differential Scanning Calorimetry

Table 7 Reported examples of solid dispersion incorporated gel [44-47]

Drug	Category	Gelling agent	Reference
Aceclofenac	NASID	HPMC	Aezaj et.al (2010)
Meloxicam	NASID	Carbopol 940	Saleen&Bala(2010)
Ketoconazole	Antifungal	Carbopol 940, Methyl cellulose	Najmuddin et.al (2010)
Ibuprofen	NSAID	Carbopol 941	Lakshmi et.al (2011)

G) Microsphere

Microspheres are solid spherical particles having range size are1-1000µm. They are spherical free flowing particles consisting of proteins or synthetic polymers. The microspheres are free flowing powders consisting of proteins or synthetic polymers, which are biodegradable in nature. There are two types of microspheres;

- ❖ Microcapsules.
- ❖ Micromatrices.

In microcapsules entrapped substance is distinctly surrounded by distinct capsule wall and in micromatrices entrapped substance is dispersing throughout the microspheres matrix. Solid biodegradable microspheres incorporating a drug dispersed or dissolved through particle matrix have the potential for the controlled release of drug. They are made from polymeric, waxy, or other protective materials (i.e. Biodegradable synthetic polymers and modified natural products).[48]

Advantages [49]

1. Constant and prolonged therapeutic effect.
2. Reduction in dosing frequency and thereby improve the patient compliance.
3. They could be injected into the body due to the spherical shape and smaller size.
4. Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
5. Microsphere morphology allows a controllable variability in degradation and drug release.

Methods of preparation of Microspheres [49]

- Emulsion solvent evaporation technique
- Emulsion cross linking method
- Coacervation method

- Spray drying technique
- Emulsion-solvent diffusion technique
- Multiple emulsion method
- Ionic gelation
- Hydroxyl appetite (HAP) microspheres in sphere morphology

Evaluation parameters [50]

1. Particle size analyzer
2. Entrapment efficiency
3. Density determination:
4. Isoelectric point
5. Angle of contact:
6. In vitro study

Table 8 Reported Examples of microsphere based gel [51-52]

Drug	Category	Gelling agent	Reference
Diclofenac sodium	NSAID	Carbopol 934	Karthikeyan et. al(2012)
Amoxicillin trihydrate	Antibacterial	Gelatin	Patel et.al.(2013)

H) Niosome

A niosome is a non-ionic surfactant-based liposome. Niosomes are formed mostly by cholesterol incorporation as an excipient. Other excipients can also be used. Niosomes have more penetrating capability than the previous preparations of emulsions. They shows structurally similarity to liposomes in having a bilayer, however, the materials used to prepare niosomes make them more stable and thus niosomes offer many more advantages over liposomes. The sizes of niosomes are microscopic and ranging from 10nm-100nm. [53]

Advantages of niosomes[54]

1. High patient compliance in comparison with oily dosage forms as the vesicle suspension is a water–based vehicle
2. Accommodate drug molecules with a wide range of solubility's
3. The characteristics of the vesicle formulation are variable and controllable.

4. The release of drug in a controlled manner.
5. They are osmotically active and stable, as well as they increase the stability of entrapped drug
6. Handling and storage of surfactants requires no special conditions
7. Improved oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs
8. They can be made to reach the site of action by oral, parenteral as well as topical routes

Methods of preparation of niosomes

1. Lipid film hydration (Hand shaking method)
2. Reverse phase evaporation
3. Microfludisation
4. Multiple membrane extrusion method
5. Ethanol injection method
6. Ether injection method
7. Sonication Method

Characterization of niosomes [53]

a. Measurement of Angle of repose
b. Scanning electron microscopy
c. Optical Microscopy
d. Measurement of vesicle size
e. Entrapment efficiency
f. Osmotic shock
g. Stability studies
h. Zeta potential analysis
i. In-vitro methods for niosomes

Table 9 Reported Examples of noisome based gel [55-57]

Drug	Category	Gelling agent	Reference
Erythromycin	Macrolide antibiotic	Carbopol 934	Vyas Jigaret al(2011)
Ketoconazole	Antifungal	Carbopol 934	Shirsand et.al.(2011)
Meloxicam	NSAID	carbopol	Srikanth K et al(2010)

EVALUATION OF GEL

Topical gel evaluated for following characters [5, 7]

- pH
- Drug contents
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- In vitro release
- Stability
- Consistency
- In vivo study

1. Measurement of pH

The pH of gel formulations are determined by digital pH meter. One gram of gel is dissolved in 100 ml distilled water and stored for two hours. The measurement of pH of each formulation is done in triplicate and average values are calculated.

2. Drug content

1 g of the prepared gel is mixed with 100ml of suitable solvent. Aliquots of different concentration are prepared by suitable dilutions after filtering the stock solution and absorbance is measured. Drug content is calculated using the equation, which is obtained by linear regression analysis of calibration curve.

3. Viscosity study

Viscosity of the prepared gel is measured byusing Brookfield Viscometer. Rotations of gel are done at 0.3, 0.6 and 1.5 rotations per minute and at each speed, the corresponding dial reading is noted. The viscosity of the gel is obtained by multiplication of the dial reading with factor given in the Brooke field Viscometer catalogues.

4. Spreadability

Good spreadability is one of the criteriafor a gel to meet the ideal properties. It is the term expressed to denote the extent of area to which gel readily spreads on application to skin or affected part. Spreading value effects on the therapeutic efficacy of a formulation. Spreadability is expressed in terms of time in seconds. It done by taken by two slides to slip off from gel and placed in between the slides under the direction of certain load. Better spread ability was shows when lesser the time taken for separation of two slides.

It is calculated by using the formula:

S = M. L / T

Where M = wt. tied to upper slide

L = length of glass slides

T = time taken to separate the slides

5. Extrudability study

The formulations are filled in the collapsible tubes after the gels are set in the container. The extrudability of the formulation is determined in terms of weight in grams required to extrude a 0.5 cm. ribbon of gel in 10 second.

6. Skin irritation study

Guinea pigs (400-500 g) of either sex are used for testing of skin irritation. The animals are maintained on standard animal feed and had free access to water. The animals are kept under standard conditions. Hair of guinea pig was shaved from back of guinea pigs and area of 4 cm2 is marked on both the sides, one side served as control while the other side is test. Gel is applied (500 mg / guinea pig) twice a day for 7 days and the site is observed for any sensitivity and the reaction if any, is graded as 0, 1, 2, 3 for no reaction, slight patchy erythema, slight but confluent or moderate but patchy erythema and severe erythema with or without edema, respectively.

7. In vitro release

The diffusion studies of the prepared gels can be carrying out in Franz diffusion cell for studying the dissolution release of gels through a cellophane membrane. Gel sample (0.5g) is taken in cellophane membrane and the diffusion studies are carried out at 37 ± 1° using 250 ml of phosphate buffer (pH 7.4) as the dissolution medium. Five milliliters of each

sample is withdrawn periodically at 1, 2, 3, 4, 5, 6, 7 and 8 h and each sample is replaced with equal volume of fresh dissolution medium. Then the samples are analyzed for the drug content by using phosphate buffer as blank.

8. Stability

The stability studies are carried out for all the gel formulation by freeze - thaw cycling. In this syneresis is observed by subjecting the product to a temperature of 4° C for 1 month, then at 25°C for 1 month, then at 40°C for 1 month. After this gel is exposed to ambient room temperature and liquid exudates separating is noted.

9. Consistency

The measurement of consistency of the prepared gels is done by dropping a cone attached to a holding rod from a fix distance of 10cm in such way that it should fall on the centre of the glass cup filled with the gel. The penetration by the cone is measured from the surface of the gel to the tip of the cone inside the gel. The distance traveled by cone is noted down after 10sec.

10. In vivo study

Inhibition of carrageenan induced rat paw odema- Three groups of 6 male wistar albino rates were used one for marketed sample (reference), other for test formulation and one group for control. The volume of unilateral hind paw test animal were measured. On each paw, 100 mg of preparation was carefully rubbed twice at 1 and 2 h. before carrageenan administration. They were placed in cages with copography meshes. 0.1 ml of 1% carrageenan was injected subcutaneously into the paw and volume of hind paw measured at hourly interval for 2 h. using a mercury plethysmometer. Percentage of inhibition was calculated.

Conclusion

Nowadays gels are getting more popular because they are more stable and also can provide controlled release. Topical gel formulation by using novel approach shows enhanced drug action and active targeting with less side effects. As topical drug delivery system bypasses the G.I. system and first pass metabolism by the liver so it can be concluded that these dosage forms serves as the best in the treatment of diseases related to the GIT.

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