



Review Article

Recent Advances in Topical Gel Formulation

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ABSTRACT

Transdermal drug delivery systems are a constant source of interest because of the benefits that they afford in overcoming many drawbacks associated with other modes of drug delivery (i.e. oral, intravenous). Topical gels are becoming more popular due to ease of application and better percutaneous absorption. Gels are semisolid formulations, which have an external solvent phase, may be hydrophobic or hydrophilic in nature, and are immobilized within the spaces of a three-dimensional network structure. Gel formulations provide better application property and stability in comparison to cream and ointments. Skin is one of the most extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system. Topical gels are intended for skin application or to certain mucosal surfaces for local action or percutaneous penetration of medicament or for their emollient or protective action. Recent studies have reported other types of gels for dermal drug application, such as proniosomal gels, emulgels, bigels and aerogels. This review is concern with all detail information regarding novel approaches to topical gel formulation, advantages and classification of gel.

Keywords: Topical gel, percutaneous absorption, Emulgel, Hydrogel.

INTRODUCTION

Topical gel is a localized drug delivery system, intended for administration into eye, rectum, vagina or skin. A gel is a solid, jelly-like material that can have properties ranging from soft and weak to hard and tough. Gels are semisolid formulations, which have an external solvent phase, may be hydrophobic or hydrophilic in nature, and are immobilized within the spaces of a three dimensional network structure. 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 gel will range in appearance from entirely clear to opaque. Most topical gels are prepared with organic polymers such as carbomers which impart an aesthetically pleasing, clear sparkling appearance to the product and are easily washed off the skin with water. Gels are two component semisolids systems rich in liquids.^{8,9} In a typical polar gel, a natural or synthetic polymer builds a three dimensional matrix throughout a hydrophilic liquid. Typical polymers used include the natural gums tragacanth, carrageenan, pectin, agar and alginic acid; semi synthetic materials such as methylcellulose, hydroxyethyl cellulose, hydroxypropylmethyl cellulose, and carboxymethylcellulose; and the synthetic polymer, carbopol may be used. Certain clays such as bentonite, veegum, and laponite provided that the drug does not bind to the polymer or clay. Gels have a broad range of applications in food, cosmetics, biotechnology, pharmatechnology, etc.

Skin is one of the most extensive and readily accessible organs on human body for topical administration and is main route of topical drug delivery system.⁷ Drug can penetrate deeper into skin and hence give better absorption. Topical preparations are applied to the skin for surface, local or systemic effects. In some cases, the base may be used alone for its therapeutic properties, such as emollient, soothing or protective action. Many topical preparations, however, contain therapeutically active ingredients which is dispersed or dissolved in the base. Topical application has many advantages over the conventional dosage forms. In general, they are deemed more effective less toxic than conventional formulations due to the bilayer composition and structure. In the formulation of topical dosage forms, attempts are being made to utilize drug carriers that ensure adequate localization or penetration of the drug within or through the skin in order to enhance the local and minimize the systemic effects, or to ensure adequate percutaneous absorption. Topical preparation avoids the GI-irritation, prevent the metabolism of drug in the liver and increase the bioavailability of the drug. Topical preparations give its action directly at the site of action.^{6,8}

PROPERTIES OF GELS

- a) It should be inert, compatible with other additives and non-toxic.
- b) It should be convenient in handling and its application
- c) It should be stable at storage condition.
- d) It should not affect biological nature of drug.
- e) Ideally, the gelling agent for pharmaceutical or cosmetic use should be inert, safe, and should not react with other formulation components.
- f) It should possess properties such as thixotropic, greaseless, emollient, non-staining etc
- g) The gelling agent included in the preparation should produce a reasonable solid-like nature during storage that can be easily broken when subjected to shear forces generated by shaking the bottle, squeezing the tube, or during topical application.
- h) It should possess suitable anti-microbial to prevent from microbial attack.
- i) The topical gel should not be tacky.⁶

CLASSIFICATION OF GEL

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

1. Based on colloidal system
 - a) 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
 - b) Single phase system (Organic)

These consist of large organic molecule existing on the twisted strands dissolved in continuous phase.
E.g. carbopol, tragacanth
2. Based on nature of solvent used
 - a) Hydrogel

Here they contain water as their continuous liquid phase
E.g. Bentonite magma, Gelatin, cellulose derivatives and poloxamer gel
 - b) Organic gel (with a non-aqueous solvent)

These contain a non -aqueous solvent as continuous phase.
E.g. plastibase (low molecular wt. polyethylene dissolved in Mineral oil & short Cooled), Olag (aerosol) gel and dispersion of metallic stearate in oils.
 - c) Xerogels

Xerogels are solid gel with low solvent concentration and produced by evaporation of solvent or freeze drying
E.g. Tragacanth ribbons, acacia tear β -cyclodextrin, dry cellulose and polystyrene.
3. Based on rheological properties

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

 - a) Plastic gels

E.g. Bingham bodies, flocculated suspensions of Aluminum hydroxide exhibit a plastic flow and the plot of rheogram gives the yield value of the gels above which the elastic gel distorts and begins to flow.
 - b) Pseudo plastic gels

E.g. Liquid dispersion of tragacanth, sodium alginate, Na CMC etc., exhibits pseudo-plastic flow. The viscosity of these gels decreases with increasing rate of shear, with no yield value.
 - c) Thixotropic gels

The bonds between particles in these gels are very weak and can be broken down by shaking. The resultant solution will revert back to gel due to the particles colliding and linking together again.
E.g. Kaolin, bentonite and agar.
4. Based on physical nature
 - a) Rigid gels

This can be formed from macromolecule in which the framework linked by primary valance bond. E.g. In silica gel, silic acid molecules are held by Si-O-Si-O bond to give a polymer structure possessing a network of pores.
 - b) Elastic gels

Gels of agar, pectin, Guar gum and alginates exhibit an elastic behavior. ^{6,7}

METHODS OF PREPARATION OF GEL

- a) Cold method
In this method the entire ingredient mixed together to form a homogenous mass, under low temperature at about 50C. 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.
- b) 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.
- c) Chemical reaction
In this method gel is produced by chemical interaction between the solute and solvent.
Eg: preparation of .silica gel and aluminium hydroxide gel
- d) 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.
- e) 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 precipitation.⁶

NOVEL APPROACHES FOR GEL FORMULATION

Emulgel

Emulgels are combination of gels and emulsions. Emulgel has emerged as promising drug delivery system for the delivery of hydrophobic drugs. Polymer can function 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, the presence of a gelling agent in the water phase converts a classical emulsion into an emulgel. These emulgel are having major advantages on novel vesicular systems as well as on conventional systems in various aspects. 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 thixotropic, greaseless, easily spreadable, easily removable, emollient, nonstaining, long shelf life, bio-friendly, transparent & pleasing appearance.^{26, 35}

Advantages

- Delivery of hydrophobic drugs
- Low preparation cost
- Better stability & better loading capacity
- Emulgels used to prolong drugs effect having short half life
- Self medication possible
- No intensive sonication is needed
- Avoidance of first pass metabolism
- Site specific drug delivery
- Improve patient compliance

Disadvantages

- Poor permeability of some drugs through skin
- Drug of large particle size not easy to absorb through skin
- Skin irritation or allergic reaction on contact dermatitis
- Occurance of bubble during emulgel preparation²⁷

Important Constituents of emulgel preparation

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.

E.g. 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.

E.g. Oleic acid (1%), lecithin(5%).^{27, 35}

Examples of emulgel

Drug	Category	Gelling agent
Miconazole Nitrate	Antifungal	Carbopol
Secnidazole	Antibacterial	Gellan gum
Ketoconazole	Antifungal	Carbopol 934 & Carbopol 940
Ciprofloxacin	Antibacterial	Poloxamer
Ibuprofen	NASID	Carbopol 940
Dimenhydrinate	Antihistamine	Gellan gum

Hydrogel

Hydrophilic gels called hydrogels are cross-linked materials absorbing large quantities of water without dissolving. Softness, smartness, and the capacity to store water make hydrogels unique materials. The ability of hydrogels to absorb water arises from hydrophilic functional groups attached to the polymer backbone while their resistance to dissolution arises from cross-links between network chains. Water inside the hydrogel allows free diffusion of some solute molecules, while the polymer serves as a matrix to hold water together. Another aspect of hydrogels is that the gel is a single polymer molecule, that is, the network chains in the gel are connected to each other to form one big molecule on macroscopic scale. It is natural to expect that the conformational transitions of the elastically active network chains become visible on the macroscopic scale of hydrogel samples. The gel is a state that is neither completely liquid nor completely solid. These half liquid-like and half solid-like properties cause many interesting relaxation behaviors that are not found in either a pure solid or a pure liquid. Some examples of Hydrogels include contact lenses, wound dressing, superabsorbents.²⁴

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

Desired physicochemical properties of drug which required for formulation of topical hydrogels are

- Drug should have a molecular weight of less than 500 Daltons.
- Drug must have adequate hydrophilicity.
- A saturated aqueous solution of the drug should have a pH value between 5 and 9.
- Drug highly acidic or alkaline in solution is not suitable for topical delivery.²⁴

Methods of preparation of hydrogels

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

Examples of hydrogel

Drug	Category	Gelling agent
Loratadine	Antihistamine	Carbopol 980
Nicotine	Stimulants	Agar
Silymarin	Antioxidant	Sodium alginate
Prazocine HCL	Antihypertensive	Sodium alginate
Diclofenac sodium	Anti-inflammatory	Sodium alginate

***In situ* gel**

In-situ forming polymeric gelling systems has become prominent among novel drug delivery system (NDDS) in recent years due to advantages such as sustained and prolonged drug action, improved patient compliance and reduced frequency of administration of the drug in comparison to conventional drug delivery system (DDS). This is a type of mucoadhesive DDS where the polymeric formulation is in sol form before administration and once comes in contact with body fluids; it undergoes gelation to form a gel. Use of various natural, biocompatible, biodegradable as well as water soluble polymers such as chitosan, glycogenic acid, poly-caprolactone, gellan gum, xyloglucan, poly-D,L-lactic acid, pluronic F127, carbopol, poly-D, L-lactide-co-glycolide and pectin makes this DDS more acceptable.^{18,19,23}

Importance of *in situ* gelling system

1. *In-situ* forming polymeric delivery system such as ease of administration & reduced frequency of administration improved patient compliance & comfort.
2. Poor bioavailability & therapeutic response exhibited by conventional ophthalmic solution due to rapid precorneal elimination of drug may be overcome by use of gel system that are instilled as drops into eye & undergoes a sol-gel transition from instilled dose.
3. Liquid dosage form that can sustain drug release & remain in contact with cornea of eye for extended period of time is ideal.
4. Reduced systemic absorption of drug drained through the nasolacrimal duct may result in some undesirable side effects.²³

Ideal characteristics of polymers

A polymer used to *in situ* gels should have following characteristics

- It should be biocompatible.
- It should be capable of adherence to mucus.
- It should have pseudo plastic behaviour.
- It should be good tolerance & optical activity.
- It should influence the tear behaviour.
- The polymer should be capable of decrease the viscosity with increasing shear rate there by offering lowered viscosity during blinking & stability of the tear film during fixation.^{18,19}

Evaluation and characterizations of *in situ* gel system

- Clarity
- Texture analysis
- Sol-Gel transition temperature and gelling time
- Gel-Strength
- Viscosity and rheology

Drug	Category	Gelling agent
Clotrimazole	Antifungal	Carbopol 934, HPMC
Indomethacin	NSAID	HPMC, Carbopol
Timolol maleate	Antiglaucoma	Carbopol
Secnidazole	Antibacterial	Gellan gum
Ofloxacin	Antibacterial	Carbopol 940
Ciprofloxacin	Antibacterial	Poloxamer

Microemulsion based gel

Microemulsion as a novel approach for topical administration of medicament or drug. 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.^{21, 26}

Advantages

- 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.³⁰

Methods of preparation

- Phase inversion method
- Phase titration method
- Evaluation of Microemulsion

Evaluation of microemulsion

- Phase behavior study
- Viscosity measurement
- Isotropic nature ^{21, 30}

Examples of microemulsion based gel

Drug	Category	Gelling agent
Tretioin	Vitamin A	Carbomer 934
Fluconazole	Antifungal	Cetyl palmitate
Ibuprofen	NSAID	Xanthan gum
Nonoxynol-9	Microbicide	Rhodigel
Bifanazole	Antifungal	HPMC
Itraconazole	Antifungal	Xanthangum, Carbopol 940

Solid Lipid Nanoparticles based gel

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.³⁹

Advantages of SLNs

- 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.³⁹

Methods of preparation for SLNs

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 method³⁹

Evaluation of SLNs

- Particle size and zeta potential
- Surface charge
- Diffusion
- Physical characterization

Examples of SLNs based gel

Drug	Category	Gelling agent
Triamcinolone	Glucocorticoids	Carbopol
Valdecoxib	Anti-inflammatory	Carbopol 934
Miconazole nitrate	Antifungal	Carbopol 934P
Aceclofenac	Antiinflammatory	Carbopol 940P, Xanthan gum, Chitoson, HPMC
Diclofenac sodium	Antiinflammatory	Carbopol 934

Ethosomes based gel:

Ethosomes are the slight modification of well established drug carrier liposome. Ethosomes are lipid vesicles containing phospholipids, alcohol (ethanol and isopropyl alcohol) in relatively high concentration and water. Ethosomes are soft vesicles made of phospholipids and ethanol (in higher quantity) and water. The size range of ethosomes may vary from tens of nanometers (nm) to microns (μ) ethosomes permeate through the skin layers more rapidly and possess significantly higher transdermal flux.^{36, 37}

Advantages of ethosomes

- Enhanced permeation of drug molecules to and through the skin to the systemic circulation
- Contrary to deformation liposomes, ethosomes improve skin delivery of drugs both under occlusive and non-occlusive conditions.
- Since composition and components of ethosomes are safe, they have various applications in pharmaceutical, veterinary and cosmetic field.
- Better patient compliance.
- Better stability and solubility of many drugs as compared to conventional vesicles.
- Relatively smaller size as compared to conventional vesicles.³⁸

Limitations of ethosomes

- Poor yield.
- In case if shell locking is ineffective then the ethosomes may coalesce and fall apart on transfer into water.
- Loss of product during transfer form organic to water media.

Methods of preparation ethosomes

1. Hot method
2. Cold method

Characterizations of Ethosomes

- Visualization
- Vesicle size and Zeta potential
- Entrapment Efficiency
- Surface Tension Activity Measurement
- Transition Temperature
- Vesicle Stability³⁸

Liposomes based gel

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 simple microscopic vesicles in which lipid bilayer structures are present with an aqueous volume entirely enclosed by a membrane, composed of lipid molecule. Liposomes present many advantages since they can be used as carriers for both hydrophilic and lipophilic molecules, as well as drug delivery systems for controlled drug delivery for different therapeutical purposes. An important aspect of liposomes is the protection that they afford as an encapsulating agent against potentially damaging conditions in external environments. 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. Liposomes are also an important system in their own right in medical, cosmetic, and industrial applications.²²

Advantages

- 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.
- Provide selective passive targeting to tumour tissues
- 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 gluco corticosteroids.
- 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 the beginning 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).²²

Methods of preparation of liposome

- Mechanical dispersion method
- Solvent dispersion method
- Detergent removal method

Characterisation of liposomes

- Size distribution
- Entrapment efficiency
- Zeta potential (z) determination
- Skin permeation and drug deposition studies
- Oscillation stress sweep Rheological studies
- Oscillation frequency sweep
- Drug content and content uniformity²²

Examples of liposome based gel

Drug	Category	Gelling agent
Fluconazole	Antifungal	Carbopol 934NF
Diclofenac sodium	Anti-inflammatory	Carbopol 934
Ketoconazole	Antifungals	Carbopol
Lidocaine	Local anesthetic	Carbopol 940
Selegiline	Monoamine oxidase inhibitor	Carbopol
Ketoprofen	NSAID	Carbopol 934

Solid Dispersion based gel

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.¹¹

Advantages of Solid Dispersion

- Reduced particle size and thus improved surface area and dissolution rate. The ultimately result in improving bioavailability.
- Wettability is improved results in increased solubility. (Carriers play the major role to improve the wettability)
- 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.
- 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.
- Rapid dissolution rates hence an increase in the rate and extent of the absorption of the drug.

Methods of preparation of solid dispersion

- Solvent evaporation method
- Hot melt extrusion
- Fusion method
- Physical mixing
- Supercritical fluid technology
- Kneading method

Evaluation & Characterization of Solid Dispersion

- Physical appearance
- Percent Practical Yield
- Drug content
- Aqueous solubility studies
- Dissolution Studies
- Drug carrier compatibility

Examples of solid dispersion incorporated gel

Drug	Category	Gelling agent
Aceclofenac	NASID	HPMC
Meloxicam	NASID	Carbopol 940
Ketoconazole	Antifungal	Carbopol 940, Methyl cellulose
Ibuprofen	NSAID	Carbopol 941

Microsphere based gel

Microspheres are small spherical particles, with diameters in the micrometer range (typically 1µm to 1000 µm). Microspheres are sometimes referred to as microparticles. 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).^{12,13}

Advantages

- Microspheres provide constant and prolonged therapeutic effect.
- Reduces the dosing frequency and thereby improve the patient compliance.
- They could be injected into the body due to the spherical shape and smaller size.
- Better drug utilization will improve the bioavailability and reduce the incidence or intensity of adverse effects.
- Microsphere morphology allows a controllable variability in degradation and drug release.^{15,16}

Disadvantages

- The modified release from the formulations.
- The release rate of the controlled release dosage form may vary from a variety of factors like food and the rate of transit through gut.
- Differences in the release rate from one dose to another.
- Controlled release formulations generally contain a higher drug load and thus any loss of integrity of the release characteristics of the dosage form may lead to potential toxicity.
- Dosage forms of this kind should not be crushed or chewed.^{12,15}

Methods of preparation of Microspheres

- Spray drying technique
- Emulsion solvent evaporation technique
- Emulsion cross linking method
- Coacervation method
- Emulsion-solvent diffusion technique
- Multiple emulsion method
- Ionic gelation
- Hydroxyl appetite (HAP) microspheres in sphere morphology^{12,13}

Evaluation parameters

- Particle size and shape
- Entrapment efficiency
- Density determination
- Isoelectric point
- Swelling Index
- Angle of contact
- In vitro study^{13,14}

Examples of microsphere based gel

Drug	Category	Gelling agent
Diclofenac sodium	SAID	Carbopol 934
Amoxicillin trihydrate	Antibacterial	Gelatin
Lidocaine hydrochloride	Local anaesthetic	Chitosan

Niosome based gel

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 show structural 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.²⁰

Advantages of niosomes

- High patient compliance in comparison with oily dosage forms as the vesicle suspension is a water-based vehicle
- Accommodate drug molecules with a wide range of solubility's
- The characteristics of the vesicle formulation are variable and controllable.
- The release of drug in a controlled manner.
- They are osmotically active and stable, as well as they increase the stability of entrapped drug
- Handling and storage of surfactants requires no special conditions
- Improved oral bioavailability of poorly absorbed drugs and enhance skin penetration of drugs

- 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. Microfluidisation
4. Multiple membrane extrusion method
5. Ethanol injection method
6. Ether injection method
7. Sonication Method.²⁰

Characterization of niosomes

- Measurement of Angle of repose
- Scanning electron microscopy
- Optical Microscopy
- Measurement of vesicle size
- Entrapment efficiency
- Osmotic shock
- Stability studies
- Zeta potential analysis
- In-vitro methods for niosomes

Examples of niosome based gel

Drug	Category	Gelling agent
Erythromycin	Macrolide antibiotic	Carbopol 934
Ketoconazole	Antifungal	Carbopol 934
Meloxicam	NSAID	Carbopol

Microsponge based gel

Microsponge is recent novel technique for control release and target specific drug delivery system. Microsponges are polymeric delivery systems composed of porous microspheres, that are mostly used for prolonged topical administration. Microsponges are designed to deliver a pharmaceutically active ingredient efficiently at minimum dose and also to enhance stability, reduce side effects, and modify drug release profiles. Microsponge technology has many favourable characteristics, which make it a versatile drug delivery vehicle. Microsponge Systems are based on microscopic, polymer-based microspheres that can suspend or entrap a wide variety of substances, and can then be incorporated into a formulated product such as a gel, cream, liquid or powder. The microsponge technology can be utilized in a variety of formulations, but is more frequently manufactured as gels. Once applied on the skin, microsponges slowly release the active agent. Microsponge do not pass through the skin (capable of holding four times their weight in skin secretions).^{1,4}

Microsponges are polymeric delivery systems consisting of porous microspheres that can entrap a wide range of active ingredients such as emollients, fragrances, essential oils, sunscreens, and anti-infective, anti-fungal, and anti-inflammatory agents. The size of the microsponges ranges from 5-300µm in diameter and a typical 25µm sphere can have up to 250000 pores and an internal pore structure equivalent to 10 feet in length, providing a total pore volume of about 1ml/g for extensive drug retention.

Characteristic of microsponge drug delivery systems

- Microsponges show acceptable stability over pH ranging from 1 to 11 and at high temperatures (up to 130°C).
- Microsponges exhibit good compatibility with various vehicles and ingredients.
- Microsponges have high entrapment efficiency up to 50 to 60%.
- Microsponges are characterized by free flowing properties.
- The average pore size of microsponges is small (0.25 µm) in a way to prevent the penetration of bacteria, thus they do not need sterilization or addition of preservatives.
- Microsponges are non-allergenic, non-irritating, non-mutagenic and non-toxic.
- Microsponges can absorb oil up to 6 times their weight without drying.^{3,4}

Advantages

- Microsponges can imbibe oil up to 6 times its weight without drying.
- Extended release.
- Improved product elegance.
- Lesser the irritation and better tolerance leads to improved patient compliance.

- Possess better thermal, physical and chemical stability.
- Non-irritating, non-mutagenic, nonallergenic and non-toxic.
- It allows the incorporation of immiscible products.
- Improved formulation flexibility.
- Free flowing and cost effective.
- Microsponges are microscopic spheres capable of absorbing skin secretions, therefore, reducing oiliness and shine from the skin.
- Microsponge formulations are self sterilizing as their average pore size is 0.25 μ m where bacteria cannot penetrate.⁵

Method of preparation of microsponge

1. Liquid-liquid suspension polymerization
2. Quasi-emulsion solvent diffusion

Evaluation of Microsponge:

- Particle size determination
- Morphology and surface topography of microsponges
- Determination of loading efficiency and production yield
- Characterization of pore structure
- Dissolution tests
- Determination of true density
- Resiliency (viscoelastic properties)^{1,4,5}

Drug enclosed in microsponge drug delivery system

- Ketoprofen
- Benzyl peroxide
- Retinol
- Fluconazole
- Ibuprofen
- Tretinoin
- Trolamine

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