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SEMISOLID DOSAGE FORM: TOPICAL GEL FORMULATION A REVIEW

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Aim/Objective: The aim of the review is to describe and understand the gel formulation and to gain knowledge about recent advance in topical gel formulation.

Dosage form

Dosage forms (also called unit doses) are pharmaceutical drug products in the form in which they are marketed for use, with a specific mixture of active ingredients and inactive components (excipients), in a particular configuration (such as a capsule shell, for example), and apportioned into a particular dose. For example, two products may both be amoxicillin, but one is in 500 mg capsules and another is in 250 mg chewable tablets. The term unit dose can also sometimes encompass non-reusable packaging as well (especially when each drug product is individually packaged), although the FDA distinguishes that by unit-dose "packaging" or "dispensing". Depending on the context, multi(ple) unit dose can refer to distinct drug products packaged together, or to a single drug product containing multiple drugs and/or doses. The term dosage form can also sometimes refer only to the pharmaceutical formulation of a drug product's constituent drug substance(s) and any blends involved, without considering matters beyond that (like how it is ultimately configured as a consumable product such as a capsule, patch, etc.). Because of the somewhat vague boundaries and unclear overlap of these terms and certain variants and qualifiers thereof within the pharmaceutical industry, caution is often advisable when conversing with someone who may be unfamiliar with another person's use of the term. Depending on the method/route of administration, dosage forms come in several types. These include many kinds of liquid, solid, and semisolid dosage forms.[1]

Semi Solid Dosage Form

The delivery of drugs on to the skin is recognized as an effective means of therapy for local dermatological disease. Over the past decades gels formed from natural, semi synthetic or synthetic polymers have been confirmed as vehicles for different types of pharmaceutical application. They have good viscosity, satisfactory bioadhesion and are without irritation or sensitizing actions.[2]

GELS

The word 'gel' is derived from 'gelatin' and both 'gel' and 'jelly' can be traced back to the Latin gelu for 'frost' and gelare, meaning 'freeze' or 'congeal'. This origin indicates the essential idea of a liquid setting to a solid like material that does not flow, but is elastic and retains some liquid characteristics.[3]

Definition

The term 'gels' is broad, encompassing semisolids of a wide range of characteristics from fairly rigid gelatin slabs, to suspensions of colloidal clays, to certain greases. Gels can be looked on as being composed of two interpenetrating phases.[4]

The USP defines gels as semisolid systems consisting of either suspension made up of small inorganic particles or large organic molecules interpenetrated by a liquid. The favorable properties of dermatological gels are thixotropic, good spreadability, greaseless, easily removed, emollient, demulcent, non-staining and comparable with number of excipients.[5]

Classification of Gels

Gels are classified in the B.P. according to the characteristics of hydrophobic or hydrophobic or hydrophilic characteristics of the gelled liquid, where as U.S.P. classified according to the number of phase's present, one or two many of these gels are thixotropic in nature forming semisolids on standing and becoming liquid on agitation.

A. **Single-phase gels:** Hydrophobic gels are also called oleo gels because their principal component is oily in nature. An example is plastibase, a liquid petroleum gel with polyethylene. This product is prepared with the aid of heat to dissolve the polymer followed by rapid cooling to form a suitable matrix. The polyethylene forms the structural matrix in the liquid petroleum resulting in a semisolid preparation. Platibase are soft, smooth, homogenized colourless, non-irritant stable vehicles. They are easily applied and

provide a velvety feel to the skin, this gel has being used as a topical base for pharmaceuticals. Hydrophillic gels contain liquid such as water, glycerin or propylene glycol. If water is the principal liquid, the gel may be called hydrogel. The wetting agents used to form the gels mostly at low concerntration, may be natural gums (acacia) synthetic polymers (carbomers) or cellulose derivatives (methyl cellulose). The method of preparation depends on gelling agents which is usually dispersed as a fine powder in the liquid. The order to avoid clumping and permit rapid hydration of the polymer. In some cases, for example, with carbomers, a base such as sodium hydroxide or an amine is added to form the gel. Hydrophilic gels are used topically for the delivery of both water soluble and water in soluble pharmaceutical. Specific examples are sodium alginate gel base and carbomer jelly.

B. **Two-phase Gels:** Hydrophobic gels contain similar liquid as the single phase hydrophobic gels, but are gelled with colloidal silica. For the preparation of hydrophilic gels the same liquids are used as single-phase gels. However inorganic polymers such as magnesium aluminium silicates or aluminium silicates are used as gelling agents. An example is bentonite magma USP.[6]

Use of Gels

The use of gels and gelling agent are quite wisdespread, even in limiting our consideration to the pharmaceutical and cosmetic fields only. Gels find use as delivery systems for oral administration as gels proper or as capsule shells made from gelatin. For topical drugs applied directly to the skin, mucous membrane, or eye and for long acting forms of drugs injected intramuscularly. Gelling agents are useful as binders in tablet granulations, protective colloids in suspensions, thickness in oral liquids and suppository bases. Commercially, gels have been employed in a wide variety of products including shampoos, fragrance products, dentrifices, skin and hair care preparations.

Characteristics of gels

Ideally, gelling agents for pharmaceutical and cosmetic use should be inert, safe and non-reactive with other formulation components. The inclusion of a gelling agent in a liquid formulation should provide a reasonable solid like nature during storage that can be broken easily squeezing a tube, or during topical application. The gel should exhibit little viscosity, changes under the temperature variation of normal use and storage. Many gels, particularly those of a polysaccharide nature are susceptible to antimicrobial degradation. Incorporation

of suitable preservative may prevent contamination and subsequent loss of gel characteristic due to microbial attack. The gel characteristics should match the intended use. A topical gel should not be tacky. Too high a concentration of gel former or the use of an excessive molecular weight may produce a gel difficult to dispense or apply. The gel characteristics should match the intended use. The aim is to produce a stable, elegant, economical gel product adequately suited for its intended use.[7]

Rheological properties

The rheological properties (study of deformation and flow of matter) are required in various pharmaceutical areas. Some of the reasons for determining rheological properties are:

1. It helps in understanding the physicochemical nature of the vehicle and the quality control of ingredients, test formulation and final products, together with manufacturing process such as mixing, milling, pumping, stirring, filling and sterilization.
2. It reflects the effects such as temperature and storage time.
3. It helps to assess a topical formulation with respect to patient usage e.g., ease of removal of preparation from the jar or tube without spillage or spreadability and adherence to the skin.
4. Finally it helps to monitor the effects of the vehicle consistency on the release of a drug from the preparation and its subsequent percutaneously penetration.

Spreadability

One of the criteria for gels to meet the ideal qualities is that it should possess good spreadability. Spreadability is a term express to denote the extent of area to which the gel readily spreads on application to skin or the affected parts. The therapeutic efficiency of a formulation also depends upon its spreading value. Hence, determination of spreadability is very important in evaluating gel characteristics. Spreadability is expressed in terms of time in seconds taken by two slides to slip-off the gel, placed in between the slides under the direction of certain load. Lesser the time taken for separation of the two slides, better the spreadability.

Extrudability

It is a useful empirical test to measure the force required to extrude the material from a deformable bottle or tube. Since the packing of gels have gained a considerable importance in

delivery of desired quantity of gel from jar or extrusion of gel from collapsible tube, therefore, measurement of extrudability becomes an important criteria for gels. While no strictly a test of the product characteristics due to inclusion of the force necessary to deform the container, the method applies shear in the region of the flow curve corresponding to a shear rate exceeding the yield value and exhibiting consequent plug flow.[8]

Gel Forming Compounds[9]

A number of polymers are used to provide the structural network that is essence of gel system. These include.

Table 1: Gelling concentration for substances used in pharmaceutical products

Gelling agent	Gel forming concentration (wt %)
NATURAL PROTEINS	
Collagen	0.2 – 0.1
Gelatin	2 – 15
POLYSACCHARIDES	
Agar	0.1 – 1
Alginates	0.5 – 1, 5 – 10
α-carragenan	1 – 2
Gellum gum (low acetyl)	0.5 – 1
Glycyrrhizin	2
Guargum	2.5 – 10
Hyaluronic acid	2
Pectin (low methoxy)	0.6 – 2
Starch	6
Tragacanth gum	2 – 5
SEMISYNTHETIC POLYMERS (CELLULOSE DERIVATIVES)	
Carboxymetyl cellulose	4 – 6, 10 – 25
Hydroxy propyl methyl cellulose	2 – 10
Hydroxy propyl cellulose	8 – 10
Metyl cellulose	2 – 4
SYNTHETIC POLYMERS	
Carbomer	0.5 – 2
Poloxamer	15 – 50
Polyacrylamide	4
Polyvinyl alcohol	10 – 20
INORGANIC SUBSTANCES	
Aluminium hydroxide	3 – 5
Bentonite	5
Hectorite	5
Laponite	2
SURFACTANTS	
Cetostearyl alcohol	10
Prij 964 (polyxyethylene alkyl ethers)	40 – 60

Methods of preparation of gel

Temperature effect

The solubility of most Lipophilic colloids e.g. Gelatin, Agar is reduced on lowering temperature, so that, cooling a concentrated hot solution will produce a gel. In contrast to this some materials such as the cellulose owe their water solubility to hydrogen bonding with water. Raising the temperature, of these solutions will disrupt the hydrogen bonding and the reduced solubility will cause gelation.

Flocculation with salts and non-solvents

Gelation is produced by adding just sufficient precipitants to produce the gel state, but insufficient to bring about complete precipitation. It is necessary to ensure rapid mixing to avoid local high concentrations of precipitant. Solution of ethyl cellulose, polysterene etc, in benzene can be gelled by rapid mixing with suitable amounts of a non-solvent such as petroleum ether. The addition of salts to hydrophobic solution to bring about coagulation and gelation is rarely observed. However, the addition of suitable proportion of salts to moderately hydrophilic solutions, such as aluminium hydroxide and bentonite produces gels. As a general rule, the addition of about half of the amount of electrolyte needed for complete precipitation is adequate. The gels formed have frequently thixotropic behavior.

Chemical reaction

In the preparation of sols by precipitation from solution e.g. Aluminium hydroxide sol. prepared by interaction in aqueous solution of an aluminium salt and sodium carbonate, an increased concentration of reactants will produce a gel structure. Silica gel is another example and is produced by the interaction of sodium silicate and acids in aqueous solution.[8]

FACTORS AFFECTING TOPICAL ABSORPTION OF DRUG

(A) Physiological Factors

1. Skin thickness.
2. Lipid content.
3. Density of hair follicles.
4. Density of sweat glands.
5. Skin pH.
6. Blood flow.
7. Hydration of skin.

8. Inflammation of skin.

(B) Physiochemical Factors

1. Partition coefficient.
2. Molecular weight (<400 dalton)
3. Degree of ionization (only unionized drugs gets absorbed well).
4. Effect of vehicles.[10]

Recent advances in Topical drugdelivery[11]

Emulgel

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.

Hydrogel

***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, glycoginic

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.

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.

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.

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.

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.

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.

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.

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

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 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.

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). 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.

Table 2: Recent advances in topical gel formulation with examples and categories.

Recent Advances	Example	Category
Emulgel	Miconazole Nitrate	Antifungal
	Secnidazole	Antibacterial
	Ketoconazole	Antifungal
	Ciprofloxacin	Antibacterial
	Ibuprofen	NASID
	Dimenhydrinate	Antihistamine
Hydrogel	Loratadine	Antihistamine
	Nicotine	Stimulants
	Silymarin	Antioxidant
	Prazocine HCL	Antihypertensive
	Diclofenac sodium	Anti-inflammatory
***In situ* gel**	Clotrimazole	Antifungal
	Indomethacin	NSAID
	Timolol maleate	Antiglaucoma
	Secnidazole	Antibacterial
	Ofloxacin	Antibacterial
	Ciprofloxacin	Antibacterial
Microemulsion based gel	Tretioin	Vitamin A
	Fluconazole	Antifungal
	Ibuprofen	NSAID
	Nonoxynol-9	Microbicide
	Bifanazole	Antifungal

	Itraconazole	Antifungal
Solid Lipid Nanoparticles based gel	Triamcinolone	Glucocorticoids
	Valdecoxib	Anti-inflammatory
	Miconazole nitrate	Antifungal
	Aceclofenac	Antiinflammatory
	Diclofenac sodium	Antiinflammatory
Liposomes based gel	Fluconazole	Antifungal
	Diclofenac sodium	Anti-inflammatory
	Ketoconazole	Antifungals
	Lidocaine	Local anesthetic
	Selegiline	Monoamine oxidase inhibitor
	Ketoprofen	NSAID
Solid Dispersion based gel	Aceclofenac	NSAID
	Meloxicam	NSAID
	Ketoconazole	Antifungal
	Ibuprofen	NSAID
Microsphere based gel	Diclofenac sodium	NSAID
	Amoxicillin trihydrate	Antibacterial
	Lidocaine hydrochloride	Local anaesthetic
Niosome based gel	Erythromycin	Macrolide antibiotic
	Ketoconazole	Antifungal
	Meloxicam	NSAID

CONCLUSION

From the over all study it can be concluded that gels can be a promising semisolid topical preparation which can be used widely.

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