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Review Paper

Recent Advances in Dermatology Semisolid Dosage Forms

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ABSTRACT:

Pharmaceutical semisolid preparations contain ointments, pastes, cream, emulsion, gels, and rigid foam. They act as carriers for drugs that are distributed topically via the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and outer ear lining. Semisolids can cling to the application surface for long sufficient periods until it is washed off. This property helps to extend the distribution of drug at the site of application. Novel semisolids are non-greasy since they consist of washable water bases. Therefore, they cause less inflammation and are superior to the traditional method of semisolid dosing. The present innovation of semisolids involves choosing an effective drug carrier system with particular focus on physicochemical properties and required therapeutic application. This article reviews the recent advances of topical dermal semisolids and its evaluation.

Keywords: Topical semisolids, hydrogels, Rheological behaviour, drug delivery system, nanoemulsions

INTRODUCTION:

Semisolids contributes to a major portion of pharmaceutical dosage forms. Widely used semisolids are ointments, creams, gels and lotions. Topical delivery is meant to be applied to the skin. It is therefore use to treat cutaneous disorders of skin. The fundamental objectives of topical delivery are restricting the pharmacological effect of the drug incorporated on to the surface or within the skin. [1]

Skin is increasingly used as a route of drug administration as it is easily accessible. The skin is composed of three layers of which epidermis offers a surface area of 100 to 1000 times greater than the other routes of absorption. It allows the applied preparation to stay intact for increased time. The stratum corneum is the outer most layer of the epidermis comprising of compacted, dead, keratinized cells in the stratified layers with a density of 1.55.[2] It plays a major role by preventing water loss from underlying tissues and also minimizes ultraviolet light penetration and limits the entrance of microorganism medication and toxic substances. It functions as a protective physical and chemical barrier layer. Beneath the stratum corneum are metabolically active layers of the epidermis. The dermis or corneum constitute the main mass of the skin. It comprises of numerous blood vessels, lymphatics, nerves and the epidermal appendages including the hair follicles, sebaceous and sweat glands.[2,3]

Route of Penetration:

When a drug system is applied topically, the drug diffuses out of its vesicle onto the surface tissues of the skin and takes the best suitable route for skin penetration. The preference for taking a specific route over different route depends only on the physicochemical properties of the drugs and the condition of the skin. Under the appropriate conditions, all the contending routes of penetration may change and play the major role. There are three potential portals of entry: transfollicular, the sweat ducts and transepidermal route. Most of molecules penetrate through skin via the inter or transfollicular route.[4]

The topical semisolids applied to skin usually in form of vehicles to elicit effect on skin surface such as emollients, antimicrobials, cleansers or as protective or occlusive dressings, an effect within stratum corneum leading to softening of the skin such as keratolytic agents. [5]

The factors that influence skin penetration are the physicochemical properties of the drug, the vehicle, pH and concentration. The absorption rate of any molecule through is inversely related to its molecular weight. The proteins and polysaccharides being molecule with high molecular weight shows poor or no penetration. The physiological variables involve the condition (intact or injured), the age, the area, the

temperature, the species variation, the moisture content and the thickness of the skin barrier tissue. The major factor affecting the rate of passage of substances penetrating skin is hydration state of stratum corneum.[5]

Dermal Semisolid Dosage forms:

Semisolid dosage forms are topical forms proposed for external application on the skin to provide local or systemic effect. It comprises of one or more combination of active substances solubilized or dispersed uniformly in a suitable medium to give stable formulation. The dermal topicals such as creams, ointments, gels and lotion permit the systemic uptake of drug incorporated in it. The topical dosage forms contain the active drug ingredient and excipient that comprise the vehicle or formulation matrix. [6]

Cream is emulsion of either oil in water or water in oil which are made thermodynamically stable by addition of suitable emulsifier. Depending upon the method and purpose of these formulation they can be classified as vanishing cream, cold cream, moisturizing cream. Water in oil type of creams have good spread ability and are less greasy whereas oil in water type of creams can be easily rub onto the skin and readily washed by water.[6,7]

Ointments are water in oil preparation that are more occlusive and meant for external application on skin or mucous membrane. They are classified according to nature of bases such as hydrocarbons bases, absorption bases, water-removable bases and water-soluble bases. Hydrocarbon bases are oleaginous base that allows the imbibition of small amount of aqueous components (eg: petrolatum)[7]. Absorption bases allows the incorporation of aqueous solution and such bases includes only anhydrous components (eg: lanolin oil, beeswax). Water removable bases are oil in water emulsion, readily washable from skin and hence widely used for cosmetic purpose (eg: emulsifying waxes). Water soluble bases are greaseless bases, formulated completely from water soluble portions (eg: polyethylene glycols).

Gel are three dimensional clear transparent semisolids acquired through hydration, homogenous dispersion and interaction of polymer. The transparent appearance is achieved by using various type pharmaceutical polymers such as hydroxypropyl cellulose, hydroxyethyl cellulose, carboxymethyl cellulose sodium. These semisolids are prepared by either fusion method or by incorporating gelling agent.[9]

Paste contains high percentage of insoluble solids that are formulated by incorporating the solids directly into a congealed system. Most commonly used powdered solids are starch, zinc oxide, calcium carbonate and talc.

Lotions are suspensions or dispersions intended for external application on to the surface of skin. It contains one or more active ingredients in an appropriate vehicle with antimicrobials, preservative and other appropriate excipients.[8]

Advances in Dermal Semisolid Dosage forms:

Formulating the semisolids involves choosing an efficacious drug carrier system with particular focus on the physicochemical properties and the required therapeutic application. In last few years, drug delivery by semisolid dosage form has seen new difficulties regarding altered drug release profile as well as improved stability of active pharmaceutical ingredients (API).[6]

Site specific drug delivery using polymeric microsphere: To reduce the applied dose of drug and frequency of administration different formulation comprising of microparticles that can easily penetrate through follicular duct needs to be formulated.[10] To overcome the above difficulties submicron emulsion vehicle system (SMEVS) has been developed that can easily penetrate through stratum corneum. The SMEVS are formulated by processing medium chain triglycerides emulsion under high pressure homogenizer followed by addition of lecithin which act as an efficient dispersing agent, resulting in reduction of droplet size usually 100-300nm. Such systems are useful for incorporating hydrophobic drugs.[11]

Hydrogels

As the name suggest water-based gel, consisting of an aqueous dispersing phase gelled with an efficient hydrophilic gelling agent are referred to as hydrogels. Hydrogels, are crosslinked 3D systems of hydrophilic polymer chains, are fit for holding a lot of water because of their hydrophilic structure. They uptake more water than 90% of their weight due to hydrophilicity, thus varying in the release systems from hydrophobic polymers.[12] Hydrogel based preparations are found to be effective in wound management. Furthermore, the biocompatibility, usability, and extraordinary flexibility of hydrogels make them undeniably fit as vehicles for delivery. As options to other drug delivery, hydrogels have been appeared to be efficacious. Various polymers such as HPMC, Carbopol, sodium alginates used as gelling agent. Hydrogel based on acrylated polxamine is utilized for delivering hydrophobic drugs and bioactive molecules. Advantages of hydrogels are they can be easily prepared, less expensive, biodegradable, versatile, many compounds can be incorporated.[13]

Deoxycholate Hydrogels:

while developing any drug carrier system, low molecular weight substances are considered as they have potential advantages when compared to polymers. These advantages such as low melt viscosity, biocompatibility, biodegradability and less toxic makes it a novel approach. Sodium deoxycholate is naturally occurring low molecular weight drug carrier acts as penetration enhancer.[14] At the point,

when the sodium deoxycholate comes in contact with abundance of buffer system, it forms thick thixotropic gel with improved penetrability. The gel leaves no remaining after application, due to its thixotropic behaviour they are easy to apply on large skin areas.[15] The surface-active property of sodium deoxycholate encourages the solubilization of several drugs by forming micelles.

Organogels:

Organogels might be viewed as bi-continuous system comprising of gelators and apolar solvent, which could possibly contain water particles captured inside self-assembled structures of gelator. They are subdivided depending on nature of gelling agent molecule i.e. polymeric or low molecular weight organogelators.[16] Various types of organogels are lecithin, PLO (Pluronic lecithin organogel), premium lecithin organogels (commonly used in bioactive agents and drug delivery), limonene GP1 also known as PG organogel. Among these PLO formulated organogel has quick absorption rate into the skin and PG organogel enhances penetration. Advantages of organogels are they are easy to prepare, cost reduction due to limited number of ingredients, they are thermodynamically stable, it consists of both hydrophobic and hydrophilic components hence suitable for incorporating both types of drug. [17]

Cream Containing Lipid Nanoparticles:

For improved penetration of topical drug, occlusion of skin is the prime basis. This necessity can be accomplished effectively by the consolidation of huge amounts of fats and oils, particularly fluid and semisolid paraffin. Nevertheless, such formulation has the constraints of poor cosmetic properties.[18] The particles of solid paraffin in water in oil cream was studied for nanodispersion formulation. These provides good occlusivity with particle mean size of 200nm. Nanoparticles were incorporated in the aqueous phase. Hence, the oil phase in which the water droplets were dispersed served as a lubricant for nanoparticles, thereby preventing a rough feel during application.[19]

Solid Lipid Nanoparticles:

Solid lipid nanoparticle (SLN) are novel drug carriers for topical use. SLN compared with polymeric nanoparticles has reduced toxicity due to the absence of solvents in the production process and reduced cost of excipients. It secures the incorporated drug against chemical degradation as there is minimal or no entry for water to enter the internal core of the lipid particle. The study investigated Prednicarbate (PC) solid lipid nanoparticles as an efficient carrier system. As a result, PC lipid nanoparticles accelerate the immediate uptake by the skin.[20]

Liposome as Drug Carriers:

Among several drug delivery systems, liposomes have demonstrated extraordinary potential as novel drug carriers for dermal and transdermal systems. Liposomes are small, spherical vesicles which contains amphiphilic lipids, encasing a hydrophilic core.[21] The lipids are predominantly phospholipids which structures bi layers similar to those found in biomembranes. The significant component of which of the liposomes are prepared is phosphatidylcholine. Liposomes shows enhance penetration of the active ingredients into epidermis and dermis, confine the drug at the site of activity, and diminish percutaneous absorption. Hence reduces the dose of a drug and achieve better therapeutic index.[21,22] One of the significant favourable advantages of using liposomes as carrier is both lipophilic as well as hydrophilic drug can be incorporated within the lipid bilayers and aqueous compartments. These applied topically gives continuous release of the drug as a result direct cooperation of drug releasing vesicle with cells at target site of the infected skin. The study of triamnicolone aceteonide (TRMA) liposome was first liposome investigated and reported by Mezei and Gulasekharam.[23] The study described TRMA liposome formulation conveyed 4,5 times more drug to epidermis and dermis when contrasted with control ointment. Various liposomal formulations containing lipid-dissolvable drugs (such as econazole, progesterone, and minoxidil) in different dose topical treatment have now been exhibited to provide a higher drug concentration; as contratsed with conventional topical delivery systems (in the form of creams, lotions, ointments and pastes). Solutions and aqueous gels are most basic form in which liposomes are applied to skin. The use of hydrophilic polymers limits the stability of liposomes as well as the rate of penetration of liposomal substances.[24,25]

Prototype liposomal formulation for skin application have few limitations such as they cannot completely penetrate into the deeper layer of skin, and affects the quality of drug to be delivered. Stratum corneum is the major barrier for drug delivery to overcome this ethosomes can be novel non-invasive delivery carriers. Ethosomes is composed of phospholipids and high concentration of and ethanol and water. The comparative study between 5% Acyclovir ethosomal preparation to that of 5% Acyclovir cream resulted in significant improvement in the treatment of herpetic infection by ethosomal formulation.[25]

Characterization of Semisolid Dosage forms:

Characterization of semisolids is most important for stable and efficient semisolid dosage form. Many mechanism interplays in their in vitro release, rheology, structural integrity and so forth, due to complex nature of semisolid network. Several new methods have been suggested for precise quantitative measurement of these parameters.

Rheological Behaviour:

Rheological properties such as viscosity and thixotropy of semisolid dosage forms are important as they can influence their drug delivery property. The rheological measurement gives detailed information about flow and deformation behaviour of dosage forms, which helps the formulator to understand quality control of raw material, final products and accordingly optimize the manufacturing processes such as homogenization speed, homogenization time, stirring speed and time, temperature. In the pharmaceutical industry, various base is used to formulate stable ointment, cream, lotion and different polymers for gels which attribute to many properties such as elasticity, yield value, texture, and viscosity.[26]

Viscometer functions are used in stress-shear rate relations for liquid; viscoelastic properties of semisolids. For non-Newtonian fluids, the shear stress versus shear rate graph is not linear as the material presents have time-dependent rheological behaviour. The shear-thinning fluids show a curve wherein an increase in shear rate results in a smaller increase in shear stress. Hence are called pseudoplastic materials. In the shear-thickening behaviour curve increase in shear stress causes smaller augment in shear rate. Three types of rheological models are accepted, based on these various semisolids can be evaluated for rheological characteristics. [28]

Petroleum jelly (petrolatum) is used as a major ingredient in a variety of topical cream and ointment formulations. The nonlinear rheological behaviour was determined using strain-controlled rheometer. It exhibits finite experience of yield stress which attributes to three-dimensional network structure that shows resistance to flow and is important in determining storage stability and sensory feature of the product.

Gel exhibit viscoelastic behaviour as it shows both liquid and solid like properties. This relation of elasticity and viscous element within polymer depends on the extent of intermolecular association-aggregation and chain entanglement. Rheological behaviour of aqueous poly(acrylic) polymer gel system was studied by static and dynamic rheometry. Poly (acrylic) polymer acts as thickener forming networked microgel structure in aqueous solution. The elastic modulus was determined which is the measure of gel rigidity. [27,29]

Gel Strength Measurement:

The mechanical assembly essentially comprises of a sample holder put on an electronic microbalance. A probe is brought down into the sample at a consistent rate. The penetration rate is estimated by the balances and recorded as an element of time. Such an increase of the mechanical resistance with which sample contradicts the bringing down of the probe. Gel quality is characterised as the proportion between the penetration force shown on the balance at specific time and the depth at which the probe has moved inside the sample simultaneously.[30,31]

In Vitro Release Study:

For topical dermatological preparations, the quality control test depends on identity, assay, rheological properties, and particle size distribution. However, these tests have limited use as they are unable to provide information drug release properties. In vitro release testing is an important tool to understand the release mechanism of an API from the semisolid dosage form. It helps to evaluate the performance and better understanding of physicochemical characteristics of the topical product. The complete dissolution of drug after its release from semisolid dosage form is explained by Higuchi diffusion equation.[33]

Plexiglas Flow-Through Cells:

In vitro drug release from semisolid dosage have been developed for studies using Plexiglas cells. The framework includes a base plate a plate containing a sample reservoir. A receptor- fluid reservoir is placed above it, and a semipermeable membrane is supported between the receptor-fluid reservoir and sample reservoir. The receptor-fluid reservoir has two equal section, one carrying the inlet and other carrying outlet for the receptor fluid. A solid Plexiglas block seals the top of the receptor-fluid reservoir. The entire cell is immersed in a constant temperature water bath. The system is automated and computer controlled by connecting it to a pump for the receptor fluid, a medium splitter, and a fraction a collector. This instrument is especially useful for measuring the effect variables such as membrane type, flow rate of a preceptor fluid, and temperature upon release rate.[35,36]

Insertion Cell:

An insertion cell is constructed such that its dimensions allow the cell to be used with compendial flow through cell. It is easier to use and does not require removal of air bubbles from the membrane-liquid interface. The upper part of the insertion cell consists of an oblong Plexiglas block with a 9mm circle cut out of it. The middle part is sample holder which consists of similar oblong long Plexiglas block with 9mm circle cut out of it and lower component is solid Plexiglas block. All three sections are screwed together. A membrane is placed between the upper section and the sample-holder section. A stainless steel spring supports the insertion cell (for the turbulent-flow mode), and a layer of glass beads in the conical section of the flow-through cell supports the insertion cell (for the laminar flow mode). The insertion cell is placed 10 mm from the conical section of the flow through cell when it is used with the spring support.

The entire assembly automated in the same way as for the Plexiglas flow through cell. [36,37]

Modified USP Type II Dissolution Apparatus:
This apparatus is used to study the in vitro release of drug from semisolid dosage form. It consists a 200ml vessel, 2.5 x 1.5cm paddle, and an enhancer diffusion cell comprises completely of Polytetrafluoroethylene. The cell contains an adjustable capacity sample reservoir, a washer for controlling the exposure to the surface area, and an open screw on cap to secure the washer and membrane over the sample reservoir. The water bath is maintained at 37ºC. Filled cells are placed in the bottom of the vessels, and paddles were lowered to 1cm above the sample surface. This system is found to yield reproducible results with good reliability in data generated. [38,40]

CONCLUSION:
In previous few years semisolid dosage form have been the focus of comprehensive research. There have been many attempts to enhance the efficiency of these system like therapeutic effectiveness of incorporated drugs or the acceptability of the formulation. This contributes not only to stable formulation but also to a favourable drug release activity. Hence more focus is given to attain comparable drug release with new drug delivery system, overcoming the unfavourable qualities of traditional semi solid dosage forms. However, liposomes are used as an appropriate drug carrier for the topical application though with variable results. It is important to review characteristics such as the rheological behaviour of dosage form and also the effect of various excipients on the rheology of formulation. There are tremendous opportunities for the production of semisolid dosage forms due to different drugs with specific features required for topical delivery.

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The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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