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SHORT COMMUNICATION

Recent Advances in Novel Semisolid Dosage Forms: An Overview

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ABSTRACT

Semisolids constitute a significant proportion of pharmaceutical dosage forms. They serve as carriers for drugs that are topically delivered by way of the skin, cornea, rectal tissue, nasal mucosa, vagina, buccal tissue, urethral membrane, and external ear lining. Novel semisolids are non-greasy since they are made up of water washable bases. Hence they cause less irritation to skin and are superior to conventional semisolid dosage form. Novel creams now a days are provided with nanoparticles and microspheres, which has an excellent emollient effect, with better spread ability, and less staining than oleaginous ointments. However both medicated and non-medicated creams provide very good emollient effects, oleaginous ointments are preferred for dry, chapped skin in an environment of low humidity because of its occlusive properties. A semisolid dosage form is advantageous in terms of its easy application, rapid formulation, and ability to topically deliver a wide variety of drug molecules.

KEY WORDS: Semisolids, Novel creams, Gel, Ointment

INTRODUCTION:

Semisolids are available as a wide range of dosage forms, each having unique characteristics (1). Ointments are semisolid preparations for external application to skin or mucous membranes. Their composition softens but does not melt upon application to the skin. Therapeutically, ointments function as skin protectives and emollients, but they are used primarily as vehicles for the topical application of drug substances. Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base, usually oil in water emulsion or aqueous microcrystalline dispersion of long-chain fatty acids or alcohols that are water-washable and are cosmetically and aesthetically acceptable. Gels are semisolid systems that consist of either suspensions of small inorganic particles or large organic molecules interpenetrated by a liquid. Gels can be either water based (aqueous gels) or organic solvent based (organogels) (2, 3). Pastes are semisolid dosage forms that contain one or more drug substances incorporated in a base with large proportions of finely dispersed solids (3, 4).

A wide range of raw materials is available for the preparation of a semisolid dosage form. Apart from the usual pharmaceutical ingredients such as preservatives, antioxidants, and solubilizes, the basic constituents of a semisolid dosage form are unique to its composition. Semisolid pharmaceutical systems comprise a body of products, which when applied to the skin or accessible mucous membranes tend to alleviate or treat a pathological condition or offer protection against a harmful environment (5, 6).

Because of their peculiar rheological behavior, semisolids can adhere to the application surface for sufficiently long periods before they are washed off. This property helps prolong drug delivery at the application site. Semisolid dosage forms usually are intended for localized drug delivery. In the past few years, however, these forms also have been explored for the systemic delivery of various drugs (1, 3, 6).

PERCUTANEOUS DRUG ABSORPTION:

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Semisolid dosage forms for dermatological drug therapy are intended to produce desired therapeutic action at specific sites in the epidermal tissue. A drug's ability to penetrate the skin's epidermis, dermis, and subcutaneous fat layers depends on the properties of the drug and the carrier base. Although some drugs are meant primarily for surface action on the skin, the target area for most dermatological disorders lies in the viable epidermis or upper dermis. Hence, a drug's diffusive penetration of the skin percutaneous absorption is an important aspect of drug therapy. The main portals of drug entry into the skin are the follicular region, the sweat ducts, or the unbroken stratum corneum between these appendages. A substance's particular route mainly depends on the physicochemical properties of the drug and the condition of the skin (7, 8).

IDEAL PROPERTIES OF NOVEL SEMISOLIDS:

1. Novel ointment bases:

a. Should absorb more water and enhance permeation.

b. When applied over skin, an oleaginous ointment film should form which prevents moisture evaporation from the skin.

c. Should not irritate skin.

2. They should be odorless, easy to handle, stable and compatible with large range of drugs and should be safe.

3. Novel semisolids should able to extend the release pattern in a controlled manner.

4. Novel semisolid should allow its use in different routes of administration with safe, odorless, easy to handle and compatible with biological membrane.

5. Use of Novel semisolids in pediatric, geriatrics and pregnant women should be safe without causing any allergic reaction.

6. Novel semisolids are safe even when applied to inflamed skin (5, 9).

TYPES OF NOVEL ADVANCES IN SEMISOLID DASAGE FORMS:

Various types of novel semisolids used are as fallow,

1. OINTMENTS (10-12):

Rectal ointment: it is used for the symptomatic relief against anal and peri-anal pruritus, pain and inflammation associated with hemorrhoids, anal fissure, fistulas and proctitis. Rectal ointment should be applied several times in a day according to the severity of the condition. For intrarectal use, apply the ointment with the help of special applicator.

2. CREAMS (11, 13, 14)

A. CREAMS CONTAINING MICROSPHERES: Albumin microsphere containing vitamin A can be administered by using creams topically. 222 ± 25 µm size of microsphere of vitamin A were produced by emulsion method. The in vitro and in vivo drug release of a microencapsulated and nonmicroencapsulated vitamin A cream was studied. The in vivo study in six volunteers revealed that these microspheres were able to remain on the skin for a long period of time, and as a consequence they were able to prolong the release of vitamin A

B. LAMELLAR FACED CREAMS: They are liquid paraffin in water emulsion prepared from cetrimide / fatty alcohol like mixed emulsifiers and ternary system formed by dispersing the mixed emulsifier in require quantity of water. The cationic emulsifying wax showed phenomenal swelling in water and this swelling was due to electrostatic repulsion which can be suppressed by addition of salt and can be reduced by changing surfactant counter ion.

C. CREAM CONTAINING LIPID NANOPARTICLES: Occlusion of cream is important criteria since it increases the penetration of topical drugs. This can be achieved by using oils and fats like liquid and semisolid paraffin in large quantities. However, such formulations have the limitations of poor cosmetic properties since they have greasy feel and glossy appearance.

The development of a water-in-oil cream containing small particles of solid paraffin was studied. A high degree of occlusivity was obtained with smooth, flexible films prepared by drying aqueous dispersions of solid paraffin particles with a mean size of 200 nm (nanoparticle dispersion).However, this nanodispersion revealed a rough texture when applied. The development of a water-in-oil cream wherein the aqueous phase was divided into small droplets solved this problem. 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.

3. GELS (11, 15, 16):

A. CONTROLLED RELEASE GELS: Drug delivery to nasal or ocular mucosa for either local or systemic action suffers from many obstacles. Gel formulations with suitable rheological and mucoadhesive properties increase the contact time at the site of absorption. However, drug release from the gel must be sustained if benefits are to be gained from the prolonged contact time.

Gelrite gels were formed in simulated tear fluid at concentrations of polymer as low as 0.1%, and it was shown that sodium was the most important gel-promoting ion in vivo. Rheology, although it may be a questionable

technique for evaluating mucoadhesive properties of polymers, showed that interactions between mucin and polymers were most likely to be seen with weak gels.

It was possible to control the release of uncharged drug substances by including surfactants that form micelles in the gel. The release depends on lipophilic interactions between the drug and the polymer and/or the micelles. Controlled-release formulations of charged drugs could be designed by mixing the drugs with oppositely charged surfactants in certain fixed ratios. In this way, vesicles in which the drug and surfactant constituted the bilayer formed spontaneously. The vesicle formation was affected by the presence of polymer, and very small vesicles that gave a slow release rate were formed when a lipophilically modified polymer was used.

The gels were also evaluated in the chamber using porcine nasal mucosa and from the results it was found that the rate of transport of drugs through the mucosa could be controlled by the rate of release from the formulation. Furthermore, the chamber can be used to evaluate the potential toxicity of formulations.

B. ORGANOGELS: Sorbitan monostearate, a hydrophobic nonionic surfactant, gels a number of organic solvents such as hexadecane, isopropyl myristate, and a range of vegetable oils. Gelation is achieved by dissolving/dispersing the organogelator in hot solvent to produce an organic solution/dispersion, which, on cooling sets to the gel state. Cooling the solution/dispersion causes a decrease in the solvent-gelator affinities, such that at the gelation temperature, the surfactant molecules self-assemble into toroidal inverse vesicles. Further cooling results in the conversion of the toroids into rod-shaped tubules. Once formed, the tubules associate with others, and a three-dimensional network is formed which immobilizes the solvent. An organogel is thus formed. Sorbitan monostearate gels are opaque, thermoreversible semisolids, and they are stable at room temperature for weeks. Such organogels are affected by the presence of additives such as the hydrophilic surfactant, polysorbate 20, which improves gel stability and alters the gel microstructure from a network of individual tubules to star-shaped "clusters" of tubules in the liquid continuous phase. Another solid monoester in the sorbitan ester family, sorbitan monopalmitate, also gels organic solvents to give opaque, thermoreversible semisolids. Like sorbitan monostearate gels, the microstructure of the palmitate gels comprises an interconnected network of rod like tubules. Unlike the stearate gels, however, the addition of small amounts of a polysorbate monoester causes a large increase in tubular length instead of the "clustering effect seen in stearate gels. The sorbitan stearate and palmitate organogels may have potential applications as delivery vehicles for drugs and antigens.

C. EXTENDED RELEASE GELS: TIMERx is a controlled release technology consists of an agglomerated, hydrophilic complex that, when compressed, forms a controlled-release matrix. The matrix, consisting of xanthan and locust bean gums (two polysaccharides) combined with dextrose, surrounds a drug core. In the presence of water, interactions between the matrix components form a tight gel while the inner core remains unwetted. The drug is encapsulated in the pores of the gel, and as the matrix travels through the patient's digestive system, the tablet swells and begins to erode. This erosion allows the drug to "back-diffuse" out through the gel-matrix at a controlled rate until the matrix erodes and a majority of the drug is released. The fundamental component controlling the rate of release lies in the properties of the gel matrix. Advantage of this system includes,

a. Predictable modified release profile like zero order or first order or initial immediate release kinetics

b. It can be manufacture on standard manufacturing equipment.

c. Cheap.

D. AMPHIPHILIC GELS: Amphiphilic gels can prepared by mixing the solid gelator like sorbitan monostearate or sorbitan monopalmitate and the liquid phase like liquid sorbitan esters or polysorbate and heating them at 60°C to form a clear isotropic sol phase, and cooling the sol phase to form an opaque semisolid at room temperature. Amphiphilic gel microstructures consisted mainly of clusters of tubules of gelator molecules that had aggregated upon cooling of the sol phase, forming a 3D network throughout the continuous phase. The gels demonstrated thermoreversibility. Gelation temperature and viscosity increased with increasing gelator concentration, indicating a more robust gel network. At temperatures near the skin surface temperature, the gels softened considerably; this would allow topical application. This study has demonstrated the formation/preparation of stable, thermoreversible, thixtropic surfactant gels (amphiphilogels) with suitable physical properties for topical use.

E. HYDROPHILIC GELS: Hydrophilic gelsare bicoherent systems composed of the internal phase made of a polymer producing a coherent three-dimensional net-like structure, which fixes the liquid vehicle as the external phase. Intermolecular forces bind the molecules of the solvent to a polymeric net, thus decreasing the mobility of these molecules and producing a structured system with increased viscosity. The physical and chemical bonds binding the particles of the internal phase provide a

relatively stable structure, which can originate by swelling of solid polymers, or by decreasing the solubility of the polymer in a solution. An important group of gels used in pharmacy are hydrophilic gels, or hydrogels, usually made of hydrophilic polymers, which under certain conditions and polymer concentration, jellify. Attention of pharmaceutical research now concentrates primarily on hydrophilic gels, as this dosage form seems to be prospective for the development of modern drugs based on systems with prolonged and controlled release of active ingredients.

F. NON AQUEOUS GELS: Ethylcellulose was successfully formulated as a nonaqueous gel with propylene glycol dicaprylate/dicaprate. The novel nonaqueous gel exhibited rheological profiles corresponding to a physically cross-linked three dimensional gel network, with suitable mechanical characteristics for use as a vehicle for topical drug delivery. Molecular conformation of the solvent was found to influence the molecular interactions associated with formation of ethylcellulose gel networks.

The gel matrices exhibited prominent viscoelastic behavior, yield stress and thixotropy. Rheological and mechanical properties showed significant upward trends with increased polymeric chain length and polymer concentrations. Good linear correlations were obtained between rheological and mechanical properties. The solvent molecular conformation was found to play a role in affecting the formation of gel networks via intermolecular hydrogen bonding between ethylcellulose polymer chains.

G. BIOADHESIVE GELS: Chitosan bioadhesive gel was formulated for nasal delivery of insulin. A nasal perfusion test was carried out to study the toxicity of four absorption enhancers like saponin, sodium deoxycholate, ethylendiamine tetra-Acetic Acid (EDTA) and lecithin. The gels contained 4000 Iu/dl insulin, 2 or 4% of low and medium molecular weight of chitosan, and lecithin or EDTA. Drug release was studied by a membraneless diffusion method and bioadhesion by a modified tensiometry test. The optimized gel was administered nasally in diabetic rats. The serum insulin levels were analyzed by an insulin enzyme immunoassay kit and serum glucose by glucose oxidase method kits. Formulations containing 2% of low molecular weight of chitosan with EDTA had higher release percentage and dissolution efficiency (DE)2.5%, lower $t_{50\%}$ (Time required to release 50% of the drug), mean dissolution time, and bioadhesion than gels containing 4% of medium molecular weight of chitosan with lecithin. Insulin was released by a zero-order kinetic from the gels. The gel of 2% medium molecular weight of chitosan with EDTA caused increase in insulin absorption and reduction the glucose level by as much as 46% of the intravenous route. Considering in vitro and in vivo studies, the formulated gel could be a useful preparation for controlled delivery of insulin through the nasal route.

H. THERMOSENSITIVE SOL-GEL REVERSIBLE HYDROGELS: They are theaqueous polymeric solutions which undergo reversible sol to gel transformation under the influence of environmental conditions like temperature and pH which results in insitu hydrogel formation.

Advantages of thermosensitive sol-gel reversible hydrogels over conventional hydrogels are,

a. It is easy to mix pharmaceutical solution rather than semisolids

b. Biocompatibility with biological systems

c. Convenient to administer

d. The pharmaceutical and biomedical uses of the such sol-gel transition include solubilization of low-molecular-weight hydrophobic drugs

e. Release can be in a controlled fashion.

f. Helps to deliver labile biomacromolecule such as proteins and genes.

g. Immobilization of cells

h. And tissue engineering

I. COMPLEXATION GELS: The goal of oral insulin delivery devices is to protect the sensitive drug from proteolytic degradation in the stomach and upper portion of the small intestine. In this work, the use of pH-responsive, poly (methacrylic-g-ethylene glycol) hydrogels as oral delivery vehicles for insulin were evaluated. Insulin was loaded into polymeric microspheres and administered orally to healthy and diabetic Wistar rats. In the acidic environment of the stomach, the gels were unswollen due to the formation of intermolecular polymer complexes. The insulin remained in the gel and was protected from proteolytic degradation. In the basic and neutral environments of the intestine, the complexes dissociated which resulted in rapid gel swelling and insulin release. Within 2 h of administration of the insulin-containing polymers, strong dose-dependent hypoglycemic effects were observed in both healthy and diabetic rats. These effects lasted for up to 8 h following administration.

EVALUATION:

1. IN-VITRO RELEASE PROFILE TEST:

The principal in vitro technique for studying skin penetration involves use of some variety of a diffusion cell like Franz cell and Flow through cell in which animal or human skin is fastened to a holder and the passage of

compounds from the epidermal surface to a fluid bath is measured (11, 17).

2. INSTRUMENTAL ANALYSIS:

A. ANALYSIS OF PHARMACEUTICAL CREAMS USING UV SPECTROPHOTOMETRY:

Solid-phase extraction (SPE) using C-18, diol and ionexchange sorbents followed by UV spectrophotometric (conventional and derivative mode) assay was applied to the analysis of basic, acidic and neutral drugs commercially available in creams. A representative set of drugs (promethazine, chlorhexidine, benzydamine, ketoprofen, ibuprofen, fentiazac, piroxicam, fluorouracil, crotamiton and hydrocortisone acetate) was selected, and for each drug the appropriate SPE conditions (adsorption, washing and elution) were investigated to obtain a practical and reliable sample clean-up.

B. GEL-STRENGTH MEASUREMENT:

Gels have gained wide acceptance as semisolid dosage forms. It has been postulated that the strength rather than the viscosity of a gel layer plays a major role in determining the amount of drug release from hydrophilic matrices. Recent advances have occurred in the development of an optimal apparatus to characterize gel strength. One proposed apparatus consists of a sample holder placed on an electronic microbalance connected to a computer. A probe is lowered into the sample by means of a motor equipped with a speed transformer, and the force required to penetrate the gel is measured. The increase in force with time is a function of the mechanical resistance of the sample to the penetration of the probe. Because the lowering speed is known, the displacement covered by the probe as a function of time is calculated and used to compute the gel-strength parameter or mechanical resistance of the gel system (13).

C. MODIFIED USP TYPE II DISSOLUTION APPARATUS:

Dissolution apparatus is modified for studying the in vitro release of phenol from ointment. It comprised a 200-mL vessel, 2.5 × 1.5 cm paddle, and an Enhancer diffusion cell (VanKel, Cary, NC). The cell contained an adjustable-capacity sample reservoir, a washer for controlling the exposure of the surface area, and an open screw-on cap to secure the washer and membrane over the sample reservoir. The water bath was maintained at 37 C. Filled cells were placed in the bottom of the vessels, and the paddles were lowered to 1 cm above the sample surface. 50 ml of highperformance liquid chromatography–grade filtered water, degassed and prewarmed to 37 0C, was used as the dissolution medium

D. ANALYSIS OF GEL USING FT-NIR TRANSMISSION SPECTROSCOPY:

Transmission Fourier transform near- infrared (FTNIR) spectroscopy was used for quantitative analysis of an active ingredient in atranslucent gel formulation. Gels were prepared using Carbopol 980 with 0%, 1%, 2%, 4%, 6%, and 8% ketoprofen and analyzed with an FT-NIR spectrophotometer operated in the transmission mode. The correlation coefficient of the calibration was 0.9996, and the root mean squared error of calibration was 0.0775%. The percent relative standard deviation for multiple measurements was 0.10%. The requirements and expectations of 2DE increase, new technologies emerge in a bid to more accurately capture the sometimes small, but significant, changes occurring in proteomics experiments. Therefore a proteomics researcher requires software that is extremely sensitive and still maintains his confidence in the analysis (11, 17).

PACKAGING OF NOVEL SEMISOLIDS:

Most semisolid products are manufacture by heating and are filled into the container while cooling still in the liquid state. It is important to established optimum pour point, the best temperature for filling and set or congealing point, the temperature at which the product become immobile in the container. Topical dermatological products are packed in either jar or tubes whereas ophthalmic, nasal, vaginal and rectal semisolid products are almost always packed in tubes.

The specific FDA regulation pertaining to drug products state that: “Container closures and other component part of drug packages, to be suitable for that intended use must not be reactive, additive or absorptive to the extent that identity, strength, quality or purity of drug will be affected”

All drug product containers and closures must be approved by stability testing of product in the final container in which it is marketed. This includes stability testing of filled container at room temperature e.g. 20^0C as well as under accelerated stability testing condition e.g. 40-50^0C.

Ointment jars are made up of clear or opaque glass or plastic. Some are colored green, amber or blue. Opaque jars are used for light sensitive products, are porcelain white, dark green or amber. Commercially available empty ointment jars vary in size from about 0.5 ounce to 1 pound. In commercial manufacture and packaging of topical products the jars and tubes are first tested for compatibility and stability for the intended product. This includes stability testing of filled containers. Tubes use to package topical pharmaceutical products are gaining in popularity since they are they are light in weight, relatively inexpensive, convenient for use, compatible with most

formulative component and provide protection against external contamination. Ointment tubes are made of aluminum or plastic. When the ointment is use for ophthalmic, rectal, vaginal or nasal application, they are packed with special applicator tips.

The multiple dose tube used for pharmaceutical has conventional continuous thread closure. Single dose tube may be prepared with a teraway tip. Meter dose, temper evident and child resistant closures are also available. Standard size of empty tubes has capacity of 1.5, 2, 3.5, 5, 15, 30, 45, 60 and 120 gm. Ointment, creams and gels are most frequently packed in 5, 15 and 30 gm tubes. Ophthalmic ointments typically are packed in small aluminum or collapsible plastic tubes holding 3.5 gm of ointment (11, 18).

DISCUSSION AND CONCLUSION:

Semisolid dosage forms have been the subject of extensive research in the past few years. Greater emphasis has been placed on achieving comparable drug release with new drug-carrier systems, eliminating the cosmetically unfavorable qualities of the conventional semisolid dosage forms. Significant attention has been placed on the exploitation of semisolid dosage forms for systemic delivery of a topically applied drug on the skin. Incorporation of drug-in-emulsion droplets of submicron size has eliminated the need for a drug's physicochemical properties to be responsible for successful drug permeation. Major efforts are being made to study characteristics such as the rheological behavior of dosage forms and the effect of various excipients on the rheology of formulation as well as the need for establishing in vitro release profiles of dosage forms. Various instruments have been proposed for this purpose and have generated reproducible and reliable results. Great opportunities for the development of semisolid dosage forms exist because of the diverse class of drugs, with unique characteristics, that are proposed for topical delivery.

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