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Recent Advances In Novel Topical Drug Delivery System

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Drug delivery systems are methods which are used to ensure that drugs get into the body and reach the area where they are needed. These systems must take a number of needs into account, ranging from ease of delivery to effectiveness of the drugs. Several companies specialize in developing methods of drug delivery, marketing these products to pharmaceutical companies, and other pharmaceutical companies develop their own systems. Many of these methods are patented and proprietary. When a drug is administered, the dosage must be carefully calculated so that the body can use the drug, which requires a drug delivery system which allows for precise dosing. Drug delivery systems also need to consider the way in which a drug is metabolized by the body. For example, some drugs are destroyed in the intestinal tract, which means that they cannot be introduced to the body in this way. Others may be dangerous in large amounts, which means that a time release method should be used to deliver the drug for patient safety. Topical drug delivery systems involve the introduction of a drug to the surface of the body, in a formulation which can be absorbed. Skin patches are an example of topical drug delivery systems. Other systems involve sprays applied to the mucus membranes of the nose, inhalation aerosols, eye drops, or creams which may be rubbed into the skin. These systems are often very easy for patients to use, which makes them appealing.In all cases, the goal of a drug delivery system is to get the right dosage to the right place. Patients tend to prefer methods which are painless and easy, which is why many pharmaceuticals come in the form of topical and enteral methods which can be taken by mouth or applied directly to the skin. In clinical environments, perenteral routes can be more common, especially for controlled substances, because these methods allow for greater control over how and when the drugs are used.

Keyword: Topical Drug Delivery Systems, Skin Patches, Skin Penetration, Localized Drug Delivery System

INTRODUCTION: Topical drug administration is a localized drug delivery system anywhere in the body through ophthalmic, rectal, vaginal and skin as topical routes.

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Skin is one of the most readily accessible organs on human body for topical administration and is main route of topical drug delivery system. This review is concern with all detail information regarding rational approach to topical formulations, principles of topical permeation and basic components of topical drug delivery systems. Overall, the clinical evidence indicates that topical gel is a safe and effective treatment

option for use in the management of skin related disease.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. The combination of active ingredients and base provides the opportunity for a wide range of topical preparations, appropriate for many types of drug delivery and therapy terms used to classify the bases of topical preparations in which therapeutically active ingredients are incorporated, may be based on their physical properties (suspension) or on their intended use (liniments) or on their composition ((hydrophilic creams).[1]Skin disease (dermatological conditions') affects at the population and has been cited as one of the top 15 medical conditions for which prevalence and healthcare spending increased in the last decade. The outcome of topical dermatological drug treatment is significantly influenced by the choice of vehicle or delivery system. Advancements in the life sciences coupled with a growing market for dermatologicals have facilitated the emergence of improved topical formulations and drug delivery systems. The current and emerging approaches of optimizing the topical delivery of dermatological agents (small and large molecules) include the use of chemical enhancers, bio-polymers (e.g. sodium hyaluronate), liposomes, particulate carriers (microspheres and lipid nanoparticles), topical sprays and foams, occlusion (via dressings and patches) topical peels, temperature (heat), iontophoresis, and ultrasound. These delivery approaches (when used solely or in a synergistic manner) are a significant improvement over conventional systems (creams, lotions, ointments and pastes) and have the potential to enhance efficacy and tolerability, improve patient compliance (including dermatology life quality), and also fulfil other unmet needs of the topical dermatological market. Non-invasive drug delivery systems provide alternative routes of administration and improved delivery of drugs to localized target sites in the body. Topically applied dermal and transdermal delivery systems could replace needles required to administer many of the new biologics-based drugs and vaccines, in addition to other significant advantages such as avoiding first-pass hepatic metabolism, gastric degradation and frequent dosing. However, the limited dermal and transdermal delivery of many small and large molecules is a significant challenge because of the unyielding barrier properties of the skin. This paper reviews the application of a novel topical delivery system, biphasic vesicles built from nanoscale components, to the delivery of several therapeutic agents and vaccine antigens and discusses progress toward clinical use

CHALLENGES OF DEVELOPING TOPICAL DRUG DELIVERY SYSTEM

The challenge of developing a successful topical product stems from the several requirements that a formulation must meet:

1. Container Selection and Product Stability

Depending on the properties of the combined ingredients, a dispensing container will be chosen (i.e., tube, jar, can, etc.) to provide a stable physicochemical environment that protects the active compound(s) from chemical degradation. The formulation can be a liquid or semi-solid, monophasic or multiphasic (e.g., oil-in-water or water-in-oil); it is largely dependent on the characteristics of the active compound(s) and on the condition of the skin to be treated.

2. Skin Penetration

Once the product is applied on the skin, a complex interaction occurs between the formulation, the active compounds, and the skin itself. The penetration of the active compound(s) into the skin follows Fick's first law of diffusion, which describes the transfer rate of solutes as a function of the concentration of the various ingredients, the size of the treatment surface area, and the permeability of the skin. However, the skin's permeability can be influenced by many factors, such as the drying, moisturizing, or occluding effects of the excipients in the

formulation, which, in combination, can modulate the release of the product at the treatment site. In acne, the site of action is inside the pilosebaceous unit and, therefore, an efficacious anti-acne formulation should facilitate the penetration of the active compound(s) into this extremely lipophilic environment.

3. Cosmetic Acceptability

In today's self-image conscious world, patients are looking for topical products that are not only safe and effective, but also cosmetically acceptable and easy to apply. This is especially true in acne, where the esthetic aspect is one of the primary reasons why patients seek dermatologic consultation. Moreover, acne patients are mainly comprised of teenagers or young adults, and therefore, products that offer convenience and are minimally disruptive to daily routines increase the level of compliance, and ultimately, the efficacy of the topical therapy. For example, vehicle considerations for prescribing should take into account the application of the drug on large, hairy surfaces like the chest and the back. This may require formulations that spread easily, or in the case of facial acne, the ideal formulation should leave minimal residue or oiliness.

Topical Route of Drug Administration

Although the intact skin is much less permeable than other tissues many substances do penetrate the skin to some degree, at relatively slow rates the penetration of the drugs and other substances through skin depends on; the physiochemical properties of the penetrant, the state of the skin and the nature of the vehicle. Drugs applied topically, mainly for local action, include anti-septic, anti-fungal, anti-inflammatory agents as well as skin emollients for protective effects. Whilst this route can also be used for systemic drug delivery.[2]Topically applied drug may diffuse through the skin by hair follicles, sweat glands or sebaceous glands but permeation through the multiple lipid bilayers of stratum corneum is the dominant pathway through the rate is very slow.[3]

Purpose of Topical Preparation

In order to formulate an effective and efficient topical preparation, consideration must be given to the intended purpose. This is directly concerned with the site of action and the desired effect of the preparation. Topical preparations may be used for: i) Surface effects: cleansing (removal of dirt and germs), cosmetic (enhancement of appearance), protective (prevention of moisture loss, sunscreen), antimicrobial (reduction of infection).

ii) Stratum corneum effects: protective (e.g. sunscreens that penetrate this layer), keratolytic (a sloughing of the skin, useful in the treatment of psoriasis), protective (moisturizing).

iii) Viable epidermal and dermal effects: several classes of drugs may penetrate to these layers (anti-inflammatory, anesthetic, antipruritic, antihistamine). Although it is difficult for drugs to penetrate the stratum corneum, once they are in the dermis, they can diffuse into the general circulation. It is difficult to formulate a drug with only a local effect without subsequent uptake by the blood.

iv) Systemic effects: a few drugs, such as scopolamine, nitroglycerin, clonidine, and estradiol, have been formulated in a manner to achieve systemic effects.

v) Appendage effects: some classes of drugs are intended to exert their action in these portions of the skin (depilatory, exfolient, antimicrobial, and antiperspirant).[1] Infection remains major cause of morbidity and mortality following the shock .phase in the burn patient. Measures to reduce the risk of wound infection and subsequent sepsis include early excision where possible, and the use of topical antimicrobial creams such as silver sulphadiazine.[4] The patient suffering major burns is at risk from both cutaneous and systemic infection.[5]

DERMATOLOGICAL BASES

Generally, topical preparations meant for systemic or local effect are classified as

Solids – Dusting powder

Semi-solids – Creams, Gel, Ointments, Paste and other
Liquids – Solution, Emulsion, Liniments, Suspension, Soaps, Shakes,
Collidons, Lotion, Paints and other.[8]

In these semi-solid formulations are more promising over solid and liquids considering its property to cling to surface of application for reasonable duration before they worn off. Pharmaceutical semi-solid preparations include ointments, pastes, cream emulsions, gel and rigid forms.[9]

Ointments

Ointments, in general, are composed of fluid hydrocarbons meshed in a matrix of higher melting solid hydrocarbons.[9]They usually contain a medicament or medicaments dissolved, suspended or emulsified in an ointment base (vehicles). There are greasy in nature.[10]

Ointment bases

The ointment base is that substance or part of an ointment, which serves as carrier or vehicle for the medicament. While selecting a suitable ointment base, the factors such as the action desired, nature of the medicament to be incorporated and the stability of an ointment are to be considered.[10]

An ideal ointment base should possess the following properties:

1. It should be inert, odorless and smooth.
2. It should be physically and chemically stable.
3. It should be compatible with the skin and with the incorporated medicaments.
4. It should be of such a consistency that it spreads and softens when applied to the skin with stress.
5. It should not retard healing of the wound.
6. It should not produce irritation or sensitization of the skin.

The United States Pharmacopoeia (USP) XX recognizes four classes of semisolids under the general classification of ointments: hydrocarbon bases, absorption bases (anhydrous form and emulsion form) water removable bases and water soluble bases.[9]

1. Hydrocarbon bases

These bases are immiscible with water and are not absorbed by the skin. There are almost inert and absorb very little water from a formulation or from skin exudates. However, they inhibit water loss from the skin by forming a waterproof film and by improving hydration, may encourage absorption of the medications through the skin.[11] Petrolatum and white ointment which is petrolatum with 5% beeswax are typical of this classes of lipophilic vehicles.[9] They are the most occlusive of the topical preparations and thus are only recommended in chronic-type skin disorders.[12]

2. Absorption bases

The absorption bases are formed by the addition of substances that are miscible with hydrocarbons and possessing polar groupings such as the sulfate, sulfonate, carboxyl, hydroxyl or an ether linkage.[9] Absorption bases may be of two types:

i) Those that permit the incorporation of aqueous solutions, resulting in the formation of water in oil emulsions. (e.g. Hydrophilic petrolatum and anhydrous lanolin)

ii) Those that are already water in oil emulsions (emulsion bases) that permit the incorporation of small, additional quantities of aqueous solutions. (E.g. Lanolin and cold cream) e.g. sodium sulfacetamide into oleaginous bases.[13]

3. Water-removable bases

Water removable bases are oil-in-water emulsions that are capable of being washed from skin or clothing with water. For this reason, they are frequently referred to as “water washable” ointment bases. These bases, which resemble creams in their appearance, may be diluted with water or with aqueous solutions. From a therapeutic viewpoint, they have the ability to

absorb serious discharges in dermatological conditions. Certain medical agents may be better absorbed by the skin when present in a base of this type than in other types of bases.[13]

4. Water-soluble bases

Water soluble vehicles are prepared from mixtures of high and low molecular weight polyethylene glycol. Suitable combinations of high and low molecular weight polyethylene glycol yield products having an ointment like consistency, which soften or melt when applied to the skin. No water is required for their preparations. These are water soluble because of the presence of many polar groups and their linkages. The "water soluble" bases are also known as greaseless ointment bases. These bases are non-toxic and non-irritating to the skin and have the advantages of being non-occlusive, miscible with exudates, non-staining and easily removed by washing.[9]

Creams

Creams are semisolid emulsion systems with opaque appearances as contrasted with translucent ointments. Their consistency and rheologic character depend on whether the emulsion is water in oil or oil-in-water type and/or the nature of the solids in the internal phase.[9] Oil-in-water emulsions are most useful as water-washable bases where as water-in-oil emulsions are emollient and cleansing. Patients often prefer water in oil cream to an ointment because the cream spreads more readily, less greasy and the evaporating water soothes the inflamed tissue. Oil in water creams (vanishing creams) rub into the skin; the continuous phase evaporates and increases the concentration of a water soluble drug in the adhering film. The concentration gradient for a drug across the stratum corneum therefore increases, promoting percutaneous absorption. To minimize drug precipitation, a formulator may include a non-volatile, water miscible co-solvent such as propylene glycol. An o/w cream is non-occlusive because it does not deposit a continuous film of water-impervious liquid. However such a cream can deposit lipids and other moisturizers on the stratum corneum and so restore the tissue's hydration ability, i.e. the preparation has emollient properties.[14]

Pastes

Pastes, like ointments, are intended for external application to the skin. They differ from ointments primarily in that they generally contain a larger percentage of solid material and as a consequence are thicker and stiffer than ointments because of their large percentage of solids. Pastes are generally more absorptive and less greasy than ointments prepared with the same components. Because of stiffness and absorptive qualities of paste, they remain in place after application with little tendency to soften and flow. Therefore these are effectively employed to absorb serous secretions from the site of application. Pastes are therefore preferred over ointments for acute lesions that have a tendency toward crusting, vesiculation or oozing. However, because of their stiffness and impenetrability, pastes are not generally suited for application to hairy part of the body. Example: zinc-oxide paste.[13]

Gels

Gels are relatively newer class of dosage forms created by entrapment of large amounts of aqueous or hydro-alcoholic liquid in a network of colloidal solid particles, which may consist of inorganic substances such as aluminum salts or organic polymers of natural or synthetic origin. Depending upon the nature of colloidal substances and the liquid in the formulation, 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.[14] Gels are two-component semisolids systems rich in liquids. 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. Such gels release medicaments well; the pores allow relatively free diffusion of molecules, which are not too large.[13]Gels are semisolid systems consisting of dispersions of small or large molecules in an aqueous liquid vehicle rendering jelly-like through the addition of gelling agent.

Among the gelling agents used are:
· Synthetic macromolecules: Carbomer 934
· Cellulosederivatives:Carboxymethylcellulose, Hydroxypropylmethyl-cellulose
Gels are compatible with many substances and may contain penetration enhancers for anti-inflammatory and anti-nauseant medications.

Types

- Single phase gels: Gels in which the macromolecules are uniformly distributed throughout a liquid with no apparent boundaries between the dispersed macromolecules and the liquid.

- Double phase gels: Gel mass consists of floccules of small distinct particles, often referred to as a magmas. Milk of magnesia (or magnesia magmas)

Jelly:[48]
Jellies are water-soluble bases prepared from natural gums such as tragacanth, pectin, alginate, and boroglycerin. Or from synthetic derivatives of natural substance such as methylcellulose and carboxymethylcellulose.

Lotion:[15]
Definition
The lotions are clear solution containing 25-50% alcohol. Additionally they may contain antiseptic, emollient, and haemostypic substance. Also they may contain extract of witchhazel, menthol, glycerin, boric acid, alum, potassium oxyquinoline sulfate & chloro form. Most of the lotions are used as after-shave preparation. Lotions are not rubbed when applied.

Types
· Hand lotion
· Face lotion
· Body lotion
· After shave lotion
· Antiperspirants lotion

Liniment:[15]
Liniments are same as lotion but they are rubbed when applied.

Suppository:[48]
Suppositories are solid dosage forms intended to deliver medicine into the rectal, vaginal, or urethral orifice. Suppositories may prepare by the cold compression or fusion technique. An appropriate base is selected for its compatibility, stability, melting point, and esthetics. Commonly used bases are cocoa butter, glycerin, hydrogenated vegetable oils, and polyethylene glycol.

Powder:[15,48]
Powder differs from liquid skin care preparation in their physical characteristics. Very fine particle size produces large surface area per unit weight, which covers a large surface area of the body & result in strong light dispersion. There are body powders, which are also known as dusting powder or talcum powder, face powder and compact. Medicated powders are used for prickly heat or preventing microbial growth on skin.

Solution:[3,49]
Solutions are liquid preparations of soluble chemicals dissolved in solvents such as water, alcohol, or propylene glycol.
· Aromatic waters
· Tinctures
· Tincture of iodine
· Sterile Indian ink for surgical procedures

Emulsion:[35,36,48,50]

Emulsions are two-phase preparations in which one phase (the dispersed or internal phase) is finely dispersed in the other (continuous or external phase). The dispersed phase can have either a hydrophobic-based (oil-in-water), or be aqueous based (water-in-oil). Because there are two incompatible phases in close conjunction, the physical stabilizing system. In most pharmaceutical emulsions, the stabilizing system comprises surfactant (ionic or nonionic), polymers (nonionic polymers, polyelectrolytes, or biopolymers), or mixtures of these.

Types

- Water-in-oil emulsion
- Oil-in-water emulsion
- Water-in-oil-in-water emulsion
- Oil-in-water-in-oil emulsion

Suspension:[31-34,48]

Suspensions are heterogeneous system consisting of two phases. The continuous or external phase is generally a liquid or semisolid and the disperse or internal phase is made up of particulate matter that is essentially insoluble in, but dispersed throughout, the continuous phase; the insoluble matter may be intended for physiologic absorption or for internal or external coating function. The dispersed phase may consist of discrete particle, or it may be a network of particles resulting from particle-particle interactions. Almost all suspension system separated on standing. The formulator's main concern, there fore, is not necessarily to try to eliminate separation, but rather to decrease the rate of settling and to permit easy resuspendability of any settled particulate matter.

A satisfactory suspension must remain sufficiently homogenous for at least the period of time necessary to remove and administered the required dose after shaking its container.

Types

- Flocculated suspension
- Deflocculated suspension

Aerosol:[48]

A system that depends on the power of compressed or liquefied gas to expel the contents from the container. The propellants responsible for developing the proper pressure within the container, and it expel the product when the valve is opened and aids in the atomization or foam production of the products. Topical pharmaceuticals aerosols utilize hydrocarbon (propane, butane, and isobutene) and compressed gases such as nitrogen, carbon dioxide, and nitrous oxide.

Other Additives Used in Semisolids

Antioxidants

Antioxidants are added to semisolid whenever oxidative deterioration is anticipated. Example: Butylated hydroxyanisole (BHA), Butylated hydroxytoluene (BHT) and EDTA.[9]

Preservatives

Preservatives are added to semisolids to prevent contamination, deterioration, and spoilage by bacteria and fungi, since many of the components in the topical preparations serve as substances for there microorganisms. Example: Mehtyl Paraben and Propyl Paraben.[11]

Humectants

Loss of water can quickly lead to skin formation in gel and humectants such as glycerol, propylene glycol or sorbitol solution may be added to retain water.[11]

Chelating agents

Bases and medicaments sensitive to heavy metals are sometimes protected by a chelating agent such as EDTA (Ethylenediamine tetra acetic acid).[11]

Perfumes

Most ointments these days have a pleasant smell imparted by incorporation of selected perfume blends. The selection of a perfume blend is very tricky business and every manufacturer would like to use one in his product. The blend selected

must be compatible with other ingredients. Example: lavender. [11] Penetration enhancer

To reduce the resistance of the stratum corneum and its biological variability, penetration enhancers (accelerants or absorption promoters) are incorporated into skin preparations. An idle penetration enhancer can be define as a chemical with the unique property in relation to skin that it reversibly reduces the barrier resistance of the horny layer without damaging any viable cells. Example: Dimethylsulfoxide (DMSO).[15]

Compounding of Ointment and Gels

Whether for large or small scale production the manufacturer of ointments generally involves either of two processes: incorporation or fusion. The method for a particular preparation depends upon the nature of the ingredients.

Incorporation

Incorporation involves the blending of an ingredient into the vehicle. This is most frequently done on a small extemporaneous scale by using either a mortar and pestle or glass slab and pair of spatulas. Stainless steel spatulas should be used if interaction between the substance and the spatula blade. In that case hard rubber spatulas should be used.

Fusion

Fusion method is used to incorporate ingredients into solids with hard properties such as waxes or spermaceti with soft oleaginous substances. Frequently, all the components are combined, melted together, and cooled with constant stirring until congealing occurs and a homogenous mixture is formed. When heat-labile substances are incorporated, those substances with the highest melting point are usually heated first and then as the liquid cools the other ingredients are added a few degrees above their respective melting points. This method prevents decomposition or volatilization of heat labile substances. On a small scale, the fusion process can be conducted in a porcelain dish or glass beaker; on a large scale it is commonly carried out in a large steam jacketed kettle. Once congealed, the ointment may be further levigated on an ointment slab or if a large volume is being prepared, a commercial mill can be used.[2]

Route of Penetration through the Skin

At the skin, molecules contact cellular debris, microorganisms, sebum and other materials, which negligibly affect permeation. The penetrant has three potential pathways to the viable tissue - through hair follicles with associated sebaceous glands, via sweat ducts, or across continuous stratum corneum between these appendages. The route usually contributes negligibly to steady state drug flux. This pathway may be important for ions and large polar molecules that struggle to cross intact stratum corneum. Appendages may be providing shunts, important at short times prior to steady state diffusion. Additionally, polymers and colloidal particles can target the follicle. The intact stratum corneum thus provides the main barrier; its 'brick and mortar' structure is analogous to a wall .The coenocytes of hydrated keratin comprise of 'bricks', embedded in 'mortar', composed of multiple lipid bilayers of cermides, fatty acids, cholesterol and cholesterol esters. These bilayers form regions of semi crystalline, gel and liquid crystals domains. Most molecules penetrate through skin via this intercellular micro route and therefore many enhancing techniques aim to disrupt or bypass elegant molecular architecture. Viable layers may metabolize a drug, or activate a prodrug. The dermal papillary layer is so rich in capillaries that most penetrant clear within minutes. Usually, deeper dermal regions do not significantly influence absorption, although they may bind e.g. testosterone, inhitibiting its systemic removal.[16]

Methods for Studying Percutaneous Absorption

The important general techniques for evaluation of percutaneous absorption can be divided into in vivo and in vitro procedures. The former uses the skin of living human or experimental animals in

situ whereas the latter employs isolated membranes and includes simple release studies.

In Vitro Methods

These are valuable techniques for screening and for measuring fluxes, partition coefficient and diffusion coefficient.

Release method without Rate – limiting membrane.

These procedures record drug release a simple immiscible phase. They measure only drug/vehicle interactions, which affect release characteristics and they do not determine skin absorption.

Diffusion methods with a rate – controlling membrane

Stimulated skin membrane: Because human skin is variable and difficult to obtain, workers use other materials, E.g. cellulose acetate, silicon rubber, isopropyl myristate, or egg shell membrane; however, these membranes are not as complex as human skin.

Natural skin membrane: Excised skin from rat, mice (normal and hairless), rabbits, guinea pigs, hamsters, pigs, hairless dogs, monkeys etc. have been mounted in diffusion cells. However, mammalian skin varies widely in stratum corneum properties and the number density appendages. Thus it is best to obtain human skin from autopsies, amputation or cosmetic surgery. Investigators use either stratum corneum or whole skin clamped in a diffusion cell and measure the amount of compound passing from the stratum corneum side through to a fluid bath.

Diffusion cells: Steady sate Flux - A well stirred donor solution at constant concentration releases penetrant through a membrane into an agitated 'sink' receptor liquid, stimulating to blood supply.

Diffusion Cells: Simulation of In vivo conditions - Cells for initiating topical therapy use an agitated receptor solution to correspond to the blood and unmixed donor phase to represent the formulation. The donor compartment may be close or open to ambient conditions or to controlled temperature and humidity; the skin may washed and material is added during an experiment. The test formulation may be a solid deposited from volatile solvent, a liquid, a semisolid, a film or a drug device. [14]

In Vivo Methods

Animal models

Most animals differ significantly from man in features that affect percutaneous absorption; the thickness and nature of stratum corneum, the density of hair follicles and sweat glands, the nature of pelt, the papillary blood supply and biochemical aspects. Few techniques produce animal disease similar to human afflictions. Thus animal models are valuable for studying the anatomy, physiology and biochemistry of skin, for screening topical agents, for detecting possible hazards, and for biopharmaceutical investigations. However experiments with animals can not substitute for human studies.

Techniques

Observation of a pharmacological response: If the drug stimulates a reaction in the viable tissue, we may use this to determine penetration kinetics. Local allergic, toxic or physiological reactions include sweat gland secretion, pigmentation and sebaceous gland activity, vasodilatation, vasoconstriction, vascular permeability, epidermal proliferation and keratinization. The most productive biopharmaceutical technique has been the vasoconstrictor or blanching response to topical steroids. Other response methods include changes in blood pressure (e.g. topical, application of nitroglycerine), and production of convulsion, reduction in the pain threshold.

Tests on Physical properties of skin: Relevant methods include measurement of transepidermal water loss, thermal determinations, mechanical analysis, use of ultrasound classification of function and dimension, spectral analysis and the use of photo acoustic and electrical properties.

Analysis of body tissue or fluids: Analysis of urine, blood, faecal matter can be used for the in vivo studies. Sometimes the drug has an affinity

for an animal organ which can be removed and analyzed e.g. for iodine, iodides and mercury. Tissue biopsy may be analyzed and even individual section measured.

Surface loss: We should be able to determine the flux of material into skin from the loss rate from the vehicle. However, because of skin impermeability, the decrease in concentration would generally be small and analytical techniques would have to be sensitive and accurate. Loss techniques have mainly been used to monitor radioactive species.

Histology: Experiments may try to locate skin penetration routes from microscopic sections; however, the cutting, handling and development of skin sections encourage leaching and translocation of materials away from their original sites, a problem with histological methods is general. Histochemical techniques have been used for those few compounds, which produce colored end products after chemical reaction. A few compounds fluoresce, revealing their behavior by microscopy e.g. vitamin A, tetracycline and benzpyrene. Tritium- labeled isotopes are useful because of their weak emissions; strong beta emitters darken areas up to 2 or 3 mm away, a great distance at cellular levels.

Stability study

Stability testing of substance, drug and drug product begins as a part of drug and synthesis or development-preformulation efforts and ends only with the demise of the compound or commercial product. FDA and ICH specifies the guidelines for stability testing of new drug products, as a technical requirement for the registration of pharmaceuticals for human use. The ICH Tripartite Guidelines have established that long term stability testing should be done at 25 C/60% RH; stress testing should be done at 40 C/75% RH for 6 months. If significant change occurs at these stress conditions, then the formulation should be tested at an intermediate condition i.e. 30 C/75%RH. The following table shows different temperatures and period of stability testing.[17]

Table 1: Storage condition for stability study`

Conditions	Temperature	Duration
Freezer Conditions	-20 to –10 C	-
Refrigerator	2 C to 8 C	-
Controlled room temperature	15 C to 30 C	Till expiry date
Accelerated temperature	40 C to 50 C	6 months

EVALUATION OF TOPICAL DOSAGE FORM

Evaluation of patch:[27]

21-day cumulative irritancy patch test:

In this test the test compound is applied daily to the same on the back or volar forearm. Test materials are applied under occlusive tape, and scores are read daily. The test application and scoring are repeated daily for 21 days or until irritation produces a predetermined maximum score. Typical erythema scores range from 0 (no visible reaction) to 4 (intense erythema with edema and vesicular erosion). Usually, 24 subjects are used in this test

Draize-shelanski repeat-insult patch test

This test is designed to measure the potential to cause sensitization. The test also provides a measure of irritancy potential. In the usual procedure the test material or a suitable dilution is applied under occlusion a 7-day rest period, the test material is applied again to a fresh site for 24 hours. The challenge sites are read on removal of the patch and again 24 hours later. The 0-4 erythema scale is used. A test panel of 100 individuals is common.

Kligman “maximization” test

This test is used to detect the contact sensitizing potential of a product or material. The test material is applied under occlusion to the same site for 48-hr periods. Prior to each exposure the site may be pretreated with a solution of sodium lauryl sulfate under occlusion. Following a 10-day interval the test material again is applied to a

different site for 48 hours under occlusion. The challenge site may be treated briefly with a sodium lauryl sulfate solution. The "maximization" test is of shorter duration and makes use of fewer test subjects than the Draize-Shelanski test.

Evaluation of ointments:[3,48]

Penetration

For assessing the penetration some very simple experiments have been suggested. Weighed quantities of the ointments are rubbed over definite areas of the skin for a given length of time. Thereafter the unabsorbed ointment is collected from the skin and weighed. The difference between the two weights roughly represents the amount absorbed.

Rate of release of medicaments

To assess the rate of release of a medicament small amount of the ointment can be placed on the surface of nutrient agar contained in a petry dish or alternately in a small cup cut in the agar surface. If the medicament is bactericidal the agar plate is previously seeded with a suitable organism like S. aureus. After a suitable period of incubation the zero of inhibition is measured and correlated with the rate of release. Another method for finding out release rate is to smear internal surface of test tubes with thin layers of ointment, fill the tubes with saline or serum and after a gap of time estimating the amount of drug present in the serum/saline.

Absorption of medicaments into blood stream

The diadermatic ointments should be evaluated for the rate of absorption of drug into the blood stream. This test can be in vivo only. Definite amounts of ointments should be rubbed the skin under standard conditions and medicaments estimated in the blood plasma or urine.

Irritant effect

In general no ointment should possess irritant effect on the skin or the skin or mucous membranes. The tests for irritancy can be carried out on the skin and eyes of rabbits or the skin in rats. Reactions are noted at intervals of 24, 48, 72 and 96 hours. Lesions on cornea, iris, conjunctiva are used for judging the irritancy to the eyes. Presence of patches on the skin within 2 weeks indicate irritancy to skin.

Evaluation of cream:[15]

Rheology

Rheology is very important as these creams are marketed in tubes or containers. The rheology or viscosity should remain constant. As these products are normally non-newtonian in nature, the viscosity can be measured using viscometers used for such liquids.

Sensitivity

As various types of ingredients are used with occasional use of antiseptic, hormones. etc., there is a possibility of sensitization or photosensitization of the skin. This should be tested beforehand. This test is normally done by patch test on skin and can be either open or occlusive. The test sample is applied along with a standard market product at different places and effect is compared after a period of time.

Biological testing

This is particularly essential for products containing antiseptics, hormones, vitamins, etc.

Evaluation of emulsions:[35,36,48]

Phase separation

The rate and degree of phase separation in an emulsion can be easily determined by keeping a certain amount in a graduated cylinder and measuring the volume of separated phase after definite time intervals. The phase separation may result from creaming or coalescence of globules. The phase separation test can be accelerated by centrifugation at low/moderate speeds. One can at best expect a mixture of creamed and coalesced particles and in such a situation it may be difficult to make correct interpretations.

Globule size

Growth in the globule size after the preparation of an emulsion is an indication of its physical instability. The globule size is measured by microscopic methods or by electronic devices such as coulter counter. In either of these two

techniques the original product has to be suitable diluted before estimation. The dilution may introduce errors because of incomplete deflocculation or new patterns of flocculation.

Rheological properties

The rheological characteristics of an emulsion system depend upon globule size, emulsifier and its concentration, phase volume ration etc. Use of a heliapath attachment with Brookfield viscometer helps in detection of creaming tendency and hence it is advisable to study rheological properties over extended periods of time, which can help in prediction of their long-term behaviour. Many emulsion show change in consistency with time which follows linear relationship when plotted on a log-log scale over a number of ten fold time intervals.

Effect of thermal stresses

It is usual to evaluate thew stability of an emulsion by subjecting it too high and low temperatures in alternating cycles. The samples are first exposed to 60 C for a few hours and then to o to 40 C. Such exposures are repeated a number of times and emulsion stability assessed after each cycle.

Evaluation of paste:[15,41,42]

Abrasiveness

The teeth were mechanically brushed with pastes or powders and then the effects were studied by observation, mechanical or other means. Abrasive character normally depended on the particle size

Particle size

This can be determined by microscopic study of the particles or other means.

Cleansing property

This is studied by measuring the change in the reflectance character of a lacquer coating on a polyester film caused by brushing with a tooth cleanser (paste or power). Also an in vivo test has been suggested in which teeth were brushed for 2 weeks and condition of teeth was assessed before and after use with the help of photographs.

Consistency

It is important that the product, paste, should maintain the consistency to enable the product press out from the container. Study of viscosity is essential for these powders from the container.

pH of the product

pH of the dispersion of 10% of the product i9n water is determined by pH meter.

Foaming character

This test is specially required for foam-forming tooth pastes or tooth pastes or tooth powers. Especially amount of product can be mixed with specific amount of and water to be shaken. The foam thus formed is studies for its nature, stability, washability.

Limit test for arsenic and lead

This is very important, as these are highly toxic metals. Specific tests are there to estimate these two metals. However, if the raw materials are tested for the limit of these two metals, products may not have excess of such metals.

Volatile matters and moisture

A specific amount of the product required to be taken in a dish and drying is to be done till constant weigh. Loss of weigh will indicate percentage of moisture and volatile matters.

Effect of special ingredients

Special tests should be done for the special ingredients if any like antiseptic, enzymes, etc. For each one special and specific test are to be done.

Evaluation of powder:[15]

Shade control and lighting

This is to control and determine the variation of color shade from batch to batch and with the stander, Proper test is to be done to prevent in shades. One such method is comparison of the appearance of the body of the power with a standard when it is spread out and flattened on a white paper background. The other method of evaluation is comparison of the sample with the standard by skin tone or undertone. Powers should be applied by the same puff that is to be used for finished pack. This is the final

judgement for the shade test. Artificial lighting is used for color evaluation.

Dispersion of color

Color should be homogeneously distributed in the power base. There should not be segregation or bleeding of color. This can be tested by spreading the power on a white paper and checking if with a magnifying glass.

Pressure testing

Pressure applied to compact powder should be uniform to the hardness can be tested by penetrometer. Reading on hardness is checked at various points of compact tablet to see the uniformity of hardness.

Breakage test

This is carried out by dropping the compact tablet of powder on a wooden surface several times from a height of 8 to 10 inches and checking the breakage or clipping of the resistance against travel and normal handling.

Flow property

This is very important, particularly for body powders, as they should come out easily from the container for easy application. This can be studied by measuring angle of repose of powder product by allowing to fall on a plate from a funnel and measuring the height and radius of heap formed.

Particle size and abrasiveness

Particle size can be determined by microscope, sieve analysis or by using sophisticated instrument and techniques. Abrasiveness can be studied by rubbing the powers on a smooth surface and then studying the effect on the surface using microscope.

Moisture content and limits for color

These can be estimated by using suitable analytical methods.

Evaluation suspension:[48]

Sedimentation volume

Measurement of the sedimentation volume and its ease of redispersion from of the most common basic evaluative procedures. The concept of sedimentation volume is simple. In short, it considers the ratio of the ultimate height (H_u) of the sediment to the initial height (H_o) of the total suspension as the suspension settles in a cylinder under standard conditions. The larger this fraction, the better is the suspendability. First obtain the H_u/H_o ratios and plot them as ordinates with time as the abscissa. Note that although the height at any particular time. The plot just described will at time zero start at 1.0, with the curve then being either horizontal or gradually sloping downward to the right as time goes on. One can compare different formulation and choose the best by observing the lines, the better formulations obviously producing lines that are more horizontal and/or less steep.

The evaluation of redispersibility is also important. To help quantitate this parameter to some extent, a mechanical shaking device may be used. It simulates human arm motion during the shaking process and can give reproducible results when used under controlled conditions.

Rheologic methods

Rheologic methods can be used to help determine the setting behavior and the arrangement of the vehicle and particle structural features for purpose of comparison. A practical rheologic method involves the use of the Brookfield viscometer mounted on a helipath stand. The T-bar spindle is made to descend slowly into the suspension, and the dial reading on the viscometer is then a measure of the resistance the spindle meets at various levels in a sediment. In this technique, the T-bar is continually changing position and measures undisturbed samples as it advances down into the suspension. This technique also indicates in which level of the suspension the structure is greater, owing to particle agglomeration, because the T-bar descends as it rotates, and the bar is continually entering new and essentially undisturbed material.

Electrokinetic techniques

Instrumentation permitted measurement of the migration velocity of the particles with respect to the surface electric charge or the familiar zeta potential; the latter has units of viscosity times electrophoretic mobility, or more familiarly, volts.

Particle size changes

The freeze-thaw cycling technique is particularly application to stressing suspension suspension for stability testing purposes. This treatment promotes particle growth and may indicate the probable future state of affairs after long storage at room temperature. Thus, it is of prime importance to be alert for changes in absolute particle size, particle size distribution, and crystal habit. Particle size distribution is sometimes determined by microscopic means. This method of necessity requires dilute suspensions that are counted with the aid of an ocular grid. In some instances, photomicrographs may to take for permanent records.

Evaluation of aerosol:[48]

Flame projection

This test indicates the effect of an aerosol formulation on the extension at an open flame. The project is sprayed for about 4 sec into a flame. Depending on the nature of the formulation, the flame is extended, the exact exact length being measured with a ruler.

Flash point

This is determined by use of the standard Tag Open Cup apparatus. The aerosol product is chilled to a temperature of about -25^0 F and transferred to the test apparatus. The test liquid is allowed to increase slowly in temperature, and the temperature at which the vapors ignite is taken as the flash point obtained is usually the flash point of the most flammable component, which in the case of topical pharmaceuticals is the hydrocarbon propellant.

Vapor pressure

The pressure can be measured simply with a pressure gauge or elaborately through use of a water bath, test gauges, and special equipment. Methods are available for aerosols packaged in both metal and glass containers.

Density

The density of an aerosol system may be accurately determined through the use of a hydrometer or a pycnometer. These methods, which have been modified to accommodate, liquefied gas preparations. A pressure tube is fitted with metal flanges and a Hoke valve, which allow for the introduction of liquids under pressure. The hydrometer is placed into the glass pressure tube. Sufficient sample is introduced through the valve to cause the hydrometer to rise halfway up the length of the tube. The density can be read directly. Specific gravity can be determined through the use of a high-pressure cylinder of about 500-ml capacity.

Moisture

Many methods have proven useful for this purpose. The Karl Fischer method has been accepted to a great extent. Gas chromatography has also been used.

Aerosol valve discharge rate

This is determined by taking an aerosol product of known weight and discharging the contents for a given period of time using standard apparatus. By reweighing the container after the time limit has expired, the discharge rate, which can then be expressed as grams per second.

Spray patterns

The method is based on the impingement of the spray on a piece of paper that has been treated with a dye-talc mixture. Depending on the nature of the aerosol, an oil-soluble or water-soluble dye is used. The particles that strike the paper cause the dye to go into solution and to be absorbed onto the paper. This gives a record of the spray, which can then be used for comparison purposes. To control the amount of material coming into contact with the paper, the paper is attached to a rotating disk that has an adjustable slit.

Dosage with metered valves

Method that can be used involves accurate weighing of filled container followed by dispensing of several doses. The container can then be reweighed, and the difference in weigh divided by the number of doses dispensed gives the average dose. This must then be repeated and the results compared. Determination of the does received by a patient is a rather difficult procedure, since all of the respiratory system has been developed and is satisfactory for this purpose.

Net contents

- The tared cans that have been placed onto the filling line are reweighed, and the difference in weigh is equal to the vet contents.
- Method is a destructive method and consists of weighing a full container and then weighed, with provision being made for the amount retained in the container.
- Opening the container and removing as much of the produce as possible. These tests are not indicated in determining the actual net weight of each container as related to the amount that can actually be dispensed.

Foam stability

The life of a foam can range from a few seconds (for some quick breaking foams) to one hour or more depending on the formulation. Several methods have been used, which include a visual evaluation, time for a given rod that is inserted into the foam to fall, and the use of rotational viscometers.

Particle size determination

Cascade impactor and "light scatter decay". The cascade impactor operates on the principle that in a stream of particles projected through a series of nozzles and glass slides at high velocity, the larger particles become impacted first on the lower velocity stages, and the smaller particles pass on and are collected at higher velocity stages. Light scatter decay method as the aerosol settles under turbulent conditions, the change in light intensity of a Tyndall beam is measured.

Evaluation of lotion:[15]

Antiseptic property

As these preparations contain antiseptics, it is necessary to evaluate antiseptic property by in-vitro test.

Determination of alcohol content

This can be determining by any suitable method as these preparations contain alcohol it is necessary to estimate the alcohol content.

Evaluation of gel:[44-48]

Drug content

1gm of gel was accurately weighed in a 50ml of volumetric flask to which 20ml purified water was added with continuous shaking. Volume was adjusted with a mixture of 10% methanol in water. Plain bases were also treated in similar manner for blank determination. Absorbance of the solution with the blank was measured at 360nm using UV-spectrophotometer.

Homogeneity of drug content

For homogeneity of drug contents, six tubes weretaken randomly and assayed for the drug content as stated above. Studies were performed in triplicate and mean values were used for the analysis of data.

Measurement of pH

The pH of carbopol gels ofTN were determined by digital pH meter. One gram of gel was dissolved in 100ml of distilled water and stored at 4°C for two hours. The measurement of pH of each formulation was in triplicate and the average values are presented.

Viscosity

Brookfield synchrolectric viscometer model RVT attached with spindle D was used for determination of viscosity. Gels were filled in jar andspindle was lowered perpendicularly taking care that spindle do not touch bottom of the jar. The spindle was rotated in the gel at increasing shear rates 0.5, 1, 2.5 and 5rpm. At each speed, the corresponding dial reading was noted. The reverse reading were also noted and average was taken for these two readings.The viscosity of the gel was obtained by the multiplication of the dial

readings with the factors given in the Brookfield viscometer catalogues.

Spreadability

A modified apparatus consisting of two glass slides containing gel in between with the lower slide fixed to a wooden plate and the upper one attached to a balance by a hook was used to determine spreadability.

Extrudability

A simple method was adopted for determination of extrudability in terms of weight in grams required to extrude a 0.5cm ribbon of gel in 10 seconds from the collapsible tube.

Evaluation of suppository:[48-54]

Melting range test

This test is also called the macro melting range test and is a measure of the time it takes for the entire suppository to melt when immersed in a constant-temperature (37C) water bath.

Liquefaction or softening time test

It consists of a U-tube partially submersed in a constant temperature water bath. A constriction on one side holds the suppository in place in tube. A glass rod is placed on top of the suppository, and the time for the rod to pass through to the constriction is recorded as the "softening time".

Breaking test

The apparatus used for the test consists of a double-wall chamber in which the test suppository is placed. Water at 37°C is pumped through the double walls of the chamber, and the suppository, contained in the dry inner chamber, supports a disc to which a rod is attached. The other end of the rod consists of another disc to which weights are applied. The test is conducted by placing 600 g on the platform. At 1-min intervals, 200-g weights are added, and the weight at which the suppository collapses is the breaking point, or the force that determines the fragility or brittleness characteristics of the suppository

Dissolution test

Testing for the rate of in vitro release of drug substances from suppositories has always posed a difficult problem, owing to melting, deformation. and dispersion in the dissolution medium. Early testing was carried out by simple placement in a beaker containing a medium. In an effort to control the variation in mass/ medium interface, various means have been employed, including a wire mesh basket, or a membrane, to separate the sample chamber from the reservoir. Samples sealed in dialysis tubing or natural membranes have also been studied. Flow cell apparatus have been used, holding the sample in place with cotton, wire screening, and most recently with glass beads.

NOVEL TOPICAL DRUG DELIVERY SYSTEM

Aerosol Foams

Aerosol foams have become an increasingly popular type of topical formulation for a variety of skin conditions including acne vulgaris. The vehicle base of the foam can have a liquid or semi-solid consistency that shares the same physicochemical characteristics of conventional vehicles like creams, lotions and gels, but it maintains desirable properties such as moisturizing/ fast-drying effects, or higher drug bioavailability. The aerosol base is dispensed through a gas-pressurized can that discharges the foam. The product characteristics (i.e., texture, bubble size and thickness, viscosity, density, persistence, stability, and spreadability) are determined by the type of formulation and the dispensing container that are selected to suit the specific treatment needs. In acne, foams may be preferred for application on large hairy surfaces (e.g., chest and back) or on the face as cleansers, because they are easier to apply.

Liposomes

Liposomes are frequently used as vehicles in pharmaceuticals and cosmetics for a controlled and optimized delivery to particular skin layers. Liposomes are spherical vesicles whose

membrane consists of amphiphilic lipids (i.e., lipids that are hydrophilic on one side and lipophilic on the other side) that enclose an aqueous core, similar to the bilayer membranes of living cells. Because liposomes offer an amphiphilic environment, they may encapsulate hydrophilic substances in their aqueous core and lipophilic substances in their lipid bilayer. This unique dual release capability enables the delivery of 2 types of substances once they are applied on the skin; each differs in its effects on skin permeability, which may enhance the desired therapeutic benefit.[4,5]

Nanoemulsions

Nanoemulsions are a class of emulsions (i.e., water-in-oil or oil-in-water formulations) that are characterized by the dispersion of very small-sized droplets when mixed. Nanoemulsions are not formed spontaneously, as they require unique thermodynamic conditions, specialized manufacturing processes, and specific surfactants that can stabilize the nano droplets. Nanoemulsions are suitable for the transport of lipophilic compounds into the skin and, therefore, they may be an ideal vehicle for use in acne to increase the penetration of the active compounds inside the lipophilic environment of the pilosebaceous unit. In addition, nanoemulsion particulates will not clog the pores and they can produce additional therapeutic effects, such as increased skin hydration and viscoelasticity.

Polymers

Polymers are large molecules consisting of repeating structural units, or monomers that are connected by covalent chemical bonds. These compounds serve as the building blocks of natural (e.g., paper and amber), biological (e.g., proteins and nucleic acid), or synthetic (e.g., plastics and polyethylene) materials. Today, applications for synthetic polymers can be found in nearly every industry, and their versatility has given rise to technological advancements within the pharmaceutical sector that address a variety of medical needs. For example, in dermatology, there are new acrylic-acid polymers that turn into a gel in the presence of water by trapping water into microcells. Inside these aqueous microcells, hydrophilic compounds can remain in a solution, whereas non-hydrophilic compounds may be dispersed in suspension. The result is a stable gel-like formulation that is easy to use and releases the active compound(s) once they are applied on the skin. Moreover, these polymer-based gels can be mixed with other excipients, such as moisturizers and emollients, to provide additional clinical benefits. Recently introduced anti-acne formulations that combine clindamycin 1% with benzoyl peroxide 5% (Duac®, Stiefel Laboratories; BenzaClin®, Dermik) utilize this novel polymer-based gel technology that exhibits efficacy and excellent tolerability.

Microsponges

Microsponges are biologically inert particles that are made of synthetic polymers with the capacity to store a volume of an active agent up to their own weight. Furthermore, the particles serve to protect the entrapped active compound from physical and environmental degradation. 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(s).

Emulsifier-free Formulations

Emulsifier-free formulations are also a growing area of development for dermatologic and cosmetic products. Most skin care products are emulsions, i.e., a mixture of 2 or more materials that are not miscible with each other; as such, according to the second law of thermodynamics, they are inherently unstable. As a result, they require the addition of surfactants (“emulsifiers”) that stabilize the formulation to guarantee an adequate shelf life. Furthermore, once these surfactant agents are applied on the skin, they tend to emulsify and remove the natural lipids of the epidermis. Consequently, the pharmaceutical industry has been developing surfactant-free emulsions as alternatives to conventional formulations by using stabilizers, such as polymeric emulsifiers or solid particles, in order to yield sufficiently stable products with a cosmetically pleasant appearance.

Fullerenes

Fullerenes are molecules composed entirely of carbon that resemble a hollow sphere. Rouse, et al., showed that once fullerenes come into contact with the skin, they migrate through the skin intercellularly, as opposed to moving through cells.8 Therefore, a fullerene could be used to "trap" active compounds and then release them into the epidermis once they are applied on the skin. Moreover, fullerenes, themselves, are thought to be potentially potent antioxidants. Data are reported in the literature showing that fullerenes are well tolerated and they hold substantial promise in dermatologic and cosmetic applications.

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