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Review Article

Topical antibiotics and Semisolid Dosage Forms

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The skin presents a first line of defence against a wide range of bacterial invaders. When the integrity of the skin is compromised accidentally or intentionally, its natural defence weaken and a role for antibacterial emerges. The topical route offers several advantages, including the avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, and the high concentration of antibacterial agent at the site of infection. Resistance to topical antibiotics is of growing concern to dermatologists. The best way of delivering the drug to skin is semisolid dosage form. In this review, we have discussed various semisolid dosage forms, advantages and disadvantages of topical delivery of drug, topical antibiotics currently available to us, and their uses in different dermatological conditions.

Key words: Semisolid, Topical, Skin, Cornium and buccal.

INTRODUCTION

Pharmaceutical semisolid preparations may be defined as topical products intended for application on the skin or accessible mucous membranes to provide localized and sometimes systemic effects at the site of application. However, most of the semisolid preparations are applied to the skin for topical relief of dermatologic conditions [1]. Semisolids 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.[2] These topical formulations are composed of drug in a suitable semisolid base which is either hydrophobic or hydrophilic in character. They contain one or more active ingredients dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity-increasing agents, antimicrobial agents, antioxidants, or stabilizing agents. The bases play an important role in determining the character of drug release. For topical antibiotics, antiseptics and deodorants, the surface microorganisms are the target. Then, effective surface bioavailability requires that the formulation should release the antimicrobial so it can penetrate the surface skin fissures and reach the organisms[3].

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 epidermis, dermis, and subcutaneous fat layers of skin depends on

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the properties of 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. 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. Semisolids are available as a wide range of dosage forms, each having unique characteristics [4].

Drug can be topically administered through skin falls into two categories: either by applying for local effect or superficial effect or for systemic effects. Local effect includes action of drug on surface of skin i.e on the epidermal layer the stratum corneum or it will modify the function of epidermis and dermis.

Advantages of topical drug delivery systems [5,6]

- Avoidance of first pass metabolism.
- Convenient and easy to apply.
- Avoidance of the risks and inconveniences of intravenous therapy and of varied conditions of absorption, like pH changes, presence of enzymes, gastric emptying time.
- Ability to easily terminate the medications, when needed.
- Ability to deliver drug more selectively to a specific site.
- Avoidance of gastro-intestinal incompatibility.
- Providing utilization of drugs with short biological half-life, narrow therapeutic window.
- Improve patient compliance.
- Provide suitability for self-medication.

Disadvantages of topical drug delivery systems[7-9]

- Skin irritation of contact dermatitis may occur due to the drug and/or excipients.
- Poor permeability of some drugs through the skin.
- Possibility of allergenic reactions.
- Drugs of larger particle size not easy to absorb through the skin

The skin represents a first line of defence against a wide range of bacterial pathogens. When the integrity of the skin is compromised accidentally or intentionally, its natural defences weaken and a role for antibacterial emerges. The topical route of application offers several advantages over systemic administration, including the avoidance of systemic toxicity and side effects, the decreased induction of bacterial resistance, and a high concentration of antibacterial agent at the site of infection. A treatment that must be physically applied to the skin is limited, however, by patient compliance, local side effects such as allergic contact dermatitis, and the depth of penetration of the agent.

Despite their shortcomings, topical antibacterial agents are highly versatile and can be used successfully for both prophylaxis and treatment of bacterial infections.

Introduction to skin infection

Skin diseases can be caused by viruses, bacteria, fungi, or parasites. The most common bacterial skin pathogens are Staphylococcus aureus and group A β-hemolytic streptococci. Herpes simplex is the most common viral skin disease. Trichophytonrubrum is the most prevalent fungi for skin disease.

Primary Infections: Primary skin infections have a characteristic clinical picture and disease course, are caused by a single pathogen, and usually affect normal skin. Impetigo, folliculitis, and boils are common types. The most common primary skin pathogens are *S aureus*, β-hemolytic streptococci, and coryneform bacteria. These organisms usually enter through a break in the skin such as an insect bite. Many systemic infections involve skin symptoms caused either by the pathogen or by toxins; examples are measles, varicella, gonococcemia, and staphylococcal scalded skin syndrome. Dermatophytic fungi have a strong affinity for keratin and therefore invade keratinized tissue of the nails, hair, and skin.

Secondary Infections: Secondary infections occur in skin that is already diseased. Because of the underlying disease, the clinical picture and course of these infections may vary. Intertrigo and toe web infection are examples.

Most skin infections cause erythema, edema, and other signs of inflammation. Focal accumulations of pus (furuncles) or fluid (vesicles, bullae) may form. Alternatively, lesions may be scaling with no obvious inflammation.

Examples of top layer skin infection:- erysipelas, folliculitis, cellulitis, hot tub folliculitis, furuncle, carbuncle, impentigo, erythrasma, etc.

Anatomy and physiology of the Skin

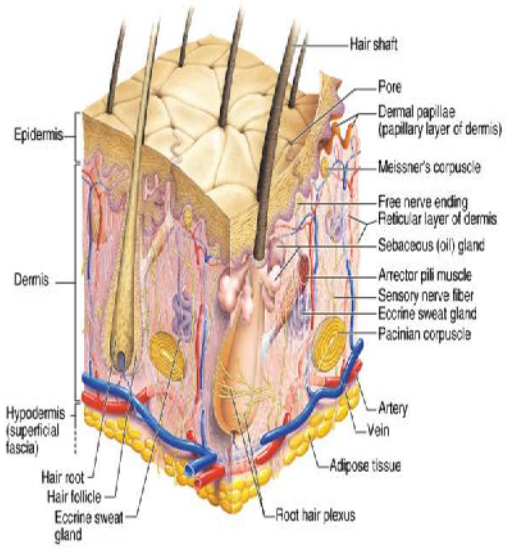

Fig. 1: Structure of skin

The skin is the largest organ of the body, accounting for about 15% of the total adult body weight. It performs many vital

functions, including protection against external physical, chemical, and biological assailants, as well as prevention of excess water loss from the body and a role in thermoregulation. The skin is continuous, with the mucous membranes lining the body's surface.

The integument system is formed by the skin and its derivative structures. The skin is composed of three layers: the outer most is epidermis, the middle dermis, and subcutaneous tissue.

1. **Epidermis**

the epidermis is the outermost layer of the skin. Catagorised into five horizontal layers.

I. **Stratum corneum**

The first or horny layer is called stratum corneum. This is top, outermost layer of epidermis and made up of flattened, dead keratinocytes. This layer is protective layer of skin. The keratinocytes rapidly sheded by friction and replaced by cells formed in deeper layer.

It is the very outer layer of epidermis, the moisture barrier and with slightly acidic pH (4.5-6.5). The acidity is due to combination of secretion from sebaceous and sweat glands. Its function is to inhibit the growth of harmful fungi and bacteria. The acidity also helps to maintain hardness of keratin protein, keeping them tightly bounded together. When the pH of the layer distrupts- the skin become prone to infection, dehydration, roughnes, irritation, and noticeable flaking.

II. **Stratum lucidium**

The second layer of epidermis is called stratum lucidium or clear layer. This layer is only present in fingertips, palms, and soles of feet.

III. **Stratum granulosum**

The third layer of epidermis is called the stratum granulosum or granular layer. It is composed of 3-5 layers of flattened keratin to tough, fibrous protein of it gives skin its protective properties.

IV. **Stratum spinosum**

The forth layer of epidermis is stratum spinosum or prikle cell layer. It is composed of 8-10 layers of polygonal keratinocytes which have thrones like end and attached to one another.

V. **Stratum germinativum**

The fifth layer of epidermis is stratum germinativum or stratum basale. This is the deepest layer and sits in dermis. It is a single layer of cube-shaped cells. The new epidermal cells called keratocytes are formed in this layer through cell division to replace those shed continuously from the upper layers of epidermis, it is regenerative process and known as cell renewal. Melanocytes are found in stratumbasale, art responsible for production of melanin which will migrate

to surface of skin and helps to porotect the skin from ultraviolet radiation.

2. **Dermis**

Just beneath the viable epidermis is the dermis. It is a structural fibrin and very few cells are like it can be found histological in normal tissue. Dermis thickness ranges from 2000 to 3000 µm and consists of a matrix of loose connective tissue composed of fibrous protein embedded in an amphorphose ground substance. It is fibrous network of tissue that provides structure and resiliencg to the skin.

3**. Hypodermis**

It is deepest section of the skin. The hypodermis refers to the fat tissue below the dermis that insulates the body from cold temperature and provide shock absorption. Fat cell of the hypodermis also store nutrients and energy. The hypodermis is the thickest in the hands, soles of the feet.

Epidermal Appendages

Sweat glands

- Eccrine Sweat Glands
- Apocrine Sweat Glands
- Eccrine Sweat Glands
- Hair follicles
- Sebaceous Glands
- Nails

Function of the skin

1. Protection:

(a) Pathogens: epidermal dendritic cells phagocytize damaged material and pathogens

(b) UV rays: melanocytes are responsible for this by producing melanin to absorb UV rays

(c) Physical or mechanical damage: stratified squamous cells are responsible for this by forming a strong protective structure

2. Reduce water loss: stratified squamous cells are filled with a tough, hydrophobic protein called keratin, that helps make the skin waterproof.

3. Thermoregulation

(a) Sweat: located in the dermis, sudoriferous glands, also known as sweat glands, allow loss of excess heat by evaporation.

(b) Shivering: contraction of skeletal muscle produces heat

(c) Fat: adipose tissue, located in the subcutaneous layer, provides a layer of insulation to conserve heat.

(d) Vasodilation/Vasoconstriction: vessels located in the dermis, dilate to allow loss of excessive heat. Or constrict when conserving heat.

4. Sensation

(a) Touch: located in the dermis, contain sensory receptors, which convey information on touch, pressure, pain, and temperature to the CNS.

5. Excretion: eliminate waste product, such as urea through sweat.

6. Vitamin D production

Route of drug penetration via skin[10]

The stratum corneum, which is its outer layer. In most of its areas, there are 10-30 layers of stacked corneocytes with palms and soles having the most. Each corneocyte is surrounded by a protein envelope and is filled with water-retaining keratin proteins. The cellular shape and orientation of the keratin proteins add strength to the stratum corneum . When a formulation is applied to the skin, several gradients are established across it, and drugs to certain extent and are able to pass through stratum corneum. It is also reported that one important factor for drugs to permeate stratum corneum is the water gradient, which can alter by application of several formulation on the skin. Hence, the effective drug delivery through the skin requires establishing external water gradient.

At the skin surface, drug molecules come in contact with cellular debris, microorganisms, and other materials, which effect permeation. The applied medicinal substance has three pathways to the viable tissue- 1) through hair follicles, 2) via sweat ducts and 3) across continuous stratum corneum between the appendages (hair follicles, sebaceous glands, eccrine, apocrine glands and nails). Fractional appendageal area available for transport is only about 0.1% and is important for ions and large polar molecules. The intact stratum corneum is the main barrier and therefore many enhancing techniques aim to disrupt or bypass this layer. Viable layers may metabolize a drug, or activate a prodrug. Usually, deeper dermal regions do not significantly influence absorption. For more than two decades, researchers have attempted to find a way to use the skin as a portal of entry for drugs in order to overcome problems associated with traditional mode of drugs administration. This route of drug delivery has gained popularity because it avoids first-pass effect, gastrointestinal irritation and metabolic degradation associated with oral administration. The topical route of administration has been utilized either to produce local effect for treating skin disorder or to produce systemic drug effects(6, 7).

In treating skin disease, the primary purpose of applying drug to the skin is to induce local effect at the site of application. In most of the cases, only a small portion of dose finally reaches the site of action, and produce limited local

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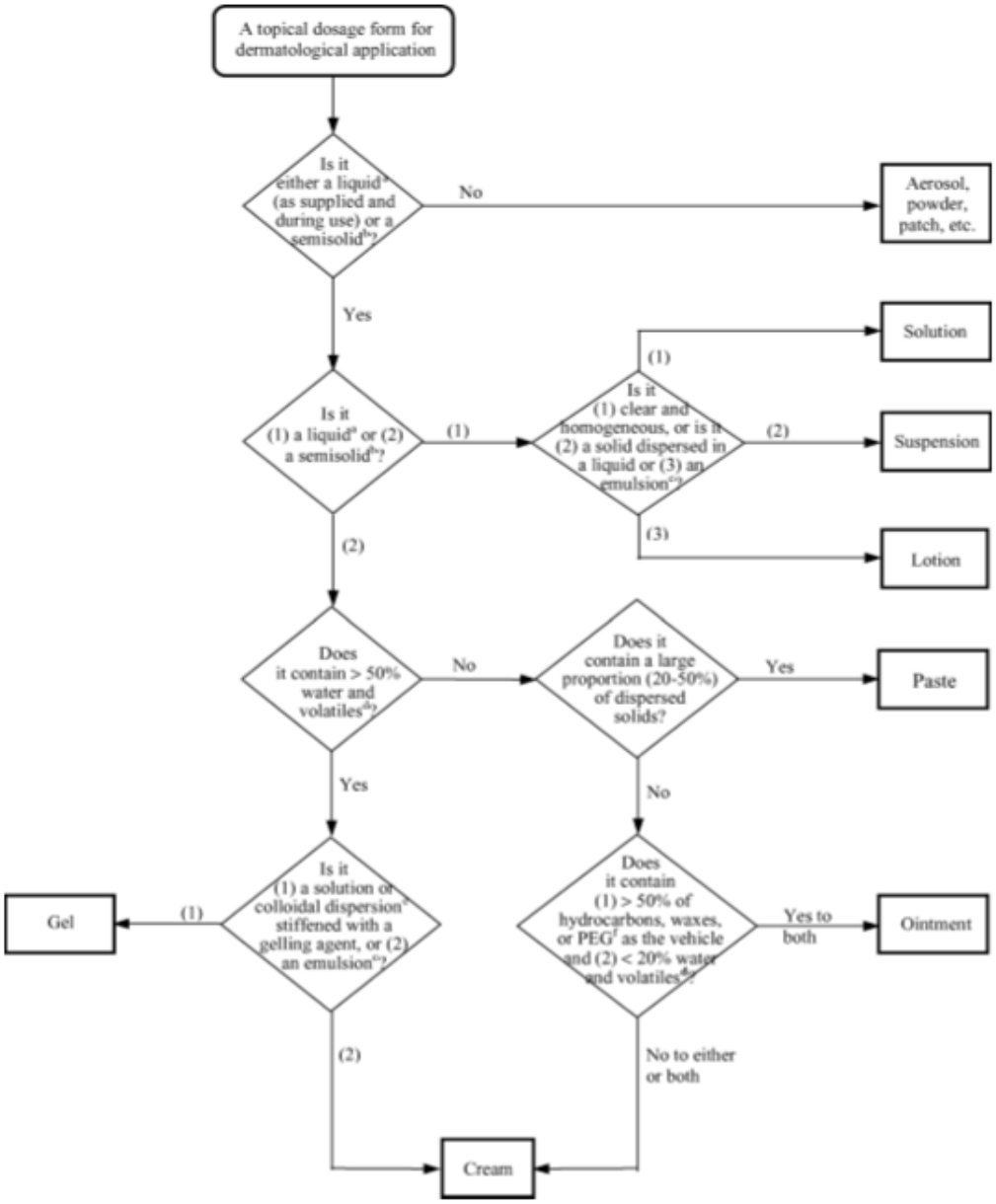

activity. This has been a complicated task due to the highly effective barrier properties of the skin.

Introduction to different types of semisolid dosage form[11]

1. Colloidion

It is a solution of nitrocellulose in ether and acetone, sometimes with the addition of alcohol. As the volatile solvents evaporate, a dry celluloid-like film of pyroxillin is left on the skin. Because the medicinal use of a collodion depends on the formation of a protective film, the film should be durable, in adherence, flexible, and occlusive.

2. Emulsion

Emulsions are viscid, multiphase systems

in which one or more liquids are dispersed throughout another immiscible liquid in the form of small droplets. When oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion. Conversely, when water or an aqueous solution is the dispersed phase and oil or oleaginous material is the continuous phase, the system is designated as a water-in-oil emulsion. Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets, and, ultimately, into a single separated phase. Emulsifying agents (surfactants) act by concentrating at the interface between the immiscible liquids, thereby providing a physical barrier that reduces the tendency for coalescence. Surfactants also reduce the interfacial tension between the phases, facilitating the formation of small droplets upon mixing. The term emulsion is not used if a more specific term is applicable, e.g., cream or ointment.

3. Ointment

Ointments are semisolids intended for external application to the skin or mucous membranes. They usually contain less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle.

Ointment bases recognized for use as vehicles fall into four general classes: hydrocarbon bases, absorption bases, water-removable bases, and water-soluble bases.

Hydrophobic ointments

Hydrophobic (lipophilic) ointments are usually anhydrous and can absorb only small amounts of water. Typical bases used for their formulation are water-insoluble hydrocarbons such as hard, soft, and liquid paraffin, vegetable oil, animal fats, waxes, synthetic glycerides, and polyalkylsiloxanes.

Water-emulsifying ointments

Water-emulsifying ointments can absorb large amounts of water. They typically consist of a hydrophobic fatty base in which a w/o agent, such as wool fat, wool alcohols, sorbitan esters, monoglycerides, or fatty alcohols can be incorporated to render them hydrophilic. They may also be w/o emulsions that allow additional quantities of aqueous solutions to be incorporated. Such ointments are used especially when formulating aqueous liquids or solutions.

Hydrophilic ointments

Hydrophilic ointment bases are miscible

Hydrophilic ointment bases are miscible with water. The bases are usually mixtures of liquid and solid polyethylene glycols (macrogols).

4. Cream

Creams are semisolid dosage forms that contain one or more drug substances dissolved or dispersed in a suitable base. This term traditionally has been applied to semisolids that possess a relatively soft, spreadable consistency formulated as either water-in-oil or oil-in-water emulsions. However, more recently the term has been restricted to products consisting of oil-in-water emulsions or aqueous microcrystalline dispersions of long-chain fatty acids or alcohols that are water washable and more cosmetically and aesthetically acceptable.

Generally, o/w creams are prepared at an elevated temperature and then cooled down to room temperature in order for the internal phase to solidify.The semi-solid form of a w/o cream is attributable to the character of the external phase.

Hydrophobic creams(w/o)

Hydrophobic creams are usually anhydrous and absorb only small amounts of water. They contain w/o emulsifying agents such as wool fat, sorbitan esters, and monoglycerides.

Hydrophilic creams(o/w)

Hydrophilic creams contain bases that are miscible with water. They also contain o/w emulsifying agents such as sodium or triethanolamine soaps, sulfated fatty alcohols, and polysorbates combined, if necessary, with w/o emulsifying agents. These creams are essentially miscible with skin secretions.

5. Foams

Foams are emulsified systems packaged in pressurized containers or special dispensing devices that contain dispersed gas bubbles, usually in a liquid continuous phase, that when dispensed has a fluffy, semisolid consistency.

6. Pastes

Pastes are semisolid dosage forms that contain a high percentage (often _ 50%) of finely dispersed solids with a stiff consistency intended for topical application. One class is made from a single-phase aqueous gel. The other class, the fatty pastes consists of thick, stiff ointments that do not ordinarily flow at body temperature and therefore serve as protective coatings over the areas to which they are applied.

7. Gel

Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid. When the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., Aluminum Hydroxide) In a two-phase system if the particle size of the dispersed phase is relatively large, the gel mass is sometimes

referred to as a magma.

Both gels and magmas may be thixotropic, forming semisolids after standing and becoming liquid when agitated. They should be shaken before use to ensure homogeneity and should be labeled to that effect. Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid with no apparent boundary between the dispersed macromolecule and liquid.

Gels are applied to the skin or certain mucous membranes for protective, therapeutic, or prophylactic purposes.

Hydrophobic gels

Hydrophobic gel (oleogel) bases usually consist of liquid paraffin with polyethylene or fatty oils gelled with colloidal silica or aluminium or zinc soaps.

Hydrophilic gels

Hydrophilic gel (hydrogel) bases usually consist of water, glycerol, or propylene glycol gelled with suitable agents such as tragacanth, starch, cellulose derivatives, carboxyvinyl polymers, and magnesium aluminium silicates.

8. Lotion

Although the term lotion may be applied to a solution, lotions usually are fluid, somewhat viscid emulsion dosage forms for external application to the skin. Lotions share many characteristics with creams.

9. Powders

Powders are solids or mixture of solids in a dry, finely divided state for external (or internal) use.

10. Sprays

Sprays are products formed by the generation of droplets of solution containing dissolved drug for application to the skin or mucous membranes. The droplets may be formed in a variety of ways but generally result from forcing the liquid through a specially designed nozzle assembly. One example of a spray dosage form is a metered-dose topical transdermal spray that delivers a precisely controlled quantity of solution or suspension on each actuation.

11. Topical Aerosols

Topical aerosols are products that are packaged under pressure. The active ingredients are released in the form of fine liquid droplets or fine powder particles upon activation of an appropriate valve system. A special form is a metered-dose aerosol that delivers an exact volume (dose) per each actuation.

12.Topical Solutions

Topical solutions are liquid preparations, that usually are aqueous but often contain other solvents such as alcohol and polyols that contain one or more dissolved chemical substances intended for topical application to the skin, or, as in the case of Lidocaine Oral Topical Solution USP, to

the oral mucosal surface.

Introduction to topical antibiotics

Topical antibiotics are medicines applied to the skin to kill bacteria. The skin is readily accessible and topical agents can be applied at high concentration, achieving effective levels locally with little systemic toxicity. The high local levels of antibiotic that can be achieved with topical formulations can help kill bacteria in bacterial biofilms.

Purpose of topical antibiotics

Topical antibiotics help to prevent infections caused by bacteria that get into minor cuts, scrapes, and burns. Treating minor wounds with antibiotics allows quicker healing. If the wounds are left untreated, the bacteria will multiply, causing pain, redness, swelling, itching, and oozing. Untreated infections can eventually spread and become much more serious. Different kinds of topical antibiotics kill different kinds of bacteria. Many antibiotic first-aid products contain combinations of antibiotics to make them effective against a broad range of bacteria.

When treating a wound, it is not enough to simply apply a topical antibiotic. The wound must first be cleaned with soap and water and patted dry. After the antibiotic is applied, the wound should be covered with a dressing, such as a bandage or a protective gel or spray. For many years, it was thought that wounds heal best when exposed to the air. But now most experts say it is best to keep wounds clean and moist while they heal. The covering should still allow some air to reach the wound, however.

Description

Some topical antibiotics are available without a prescription and are sold in many forms, including creams, ointments, powders, and sprays. Some widely used topical antibiotics are bacitracin, neomycin, mupirocin, and polymyxin B. Among the products that contain one or more of these ingredients are Bactroban (a prescription item), Neosporin, Polysporin, and Triple Antibiotic Ointment or Cream.

Recommended Dosage

It depends on the type of topical antibiotic being used. In general, they should be applied within four hours after injury.

Precautions

Many public health experts are concerned about antibiotic resistance, a problem that can develop when antibiotics are overused. Over time, bacteria develop new defenses against antibiotics that once were effective against them. Because, bacteria reproduce so quickly, these defenses can be rapidly passed on through generations of bacteria until almost all are immune to the effects of a particular antibiotic. The process happens faster [12]than new antibiotics

can be developed. To help control the problem, many experts advise people to use topical antibiotics only for short periods, that is, until the wound heals, and only as directed. For the topical antibiotic to work best, it should be used only to prevent infection in a fresh wound, not to treat an infection that has already started. Wounds that are not fresh may need the attention of a physician to prevent complications such as blood poisoning.

Topical antibiotics are meant to be used only on the skin and only for only a few days at a time. Do not use topical antibiotics on large areas of skin or on open wounds. These products should not be used to treat diaper rash in infants or incontinence rash in adults.

Only minor cuts, scrapes, and burns should be treated with topical antibiotics. Certain kinds of injuries may need medical care and should not be self-treated with topical antibiotics. These include: large wounds •deep cuts •cuts that continue bleeding •cuts that may need stitches •burns any larger than a few inches in •diameter scrapes imbedded with particles that won't •wash away animal bites •deep puncture wounds •eye injuries etc.

Although topical antibiotics control infections caused by bacteria, they may allow fungal infections to develop. The use of other medicines to treat the fungal infections may be necessary. Some people may be allergic to one or more ingredients in a topical antibiotic product. No harmful or abnormal effects have been reported in babies whose mothers used topical antibiotics while pregnant or nursing. However, pregnant women generally are advised not to use any drugs during the first 3 months after conception.

Side Effects

The most common minor side effects are itching or burning. These problems usually do not require medical treatment unless they do not go away or they interfere with normal activities. Other reported side effects are as follows:

- Rash
- swelling of the lips and face
- sweating
- tightness or discomfort in the chest• breathing problems• fainting or •dizziness low blood pressure
- nausea
- diarrhoea
- hearing loss or ringing in the ears
- Other rare side effects may occur.

Interactions

Using certain topical antibiotics at the same time as hydrocortisone (a topical corticosteroid used to treat inflammation) may hide signs of infection or allergic reaction.

Common Topical Antibiotics used in

Dermatology

The general topical antibiotics used are bacitracin, mupirocine, gentamycin, neomycin sulphate, erythromycin, Dapson, polymixin, fusidic acid, etc.

Bacitracin A

Complex of cyclic peptide antibiotics produced by the Tracy-I strain of Bacillus subtilis. The commercial preparation is a mixture of at least nine bacitracins with bacitracin A as the major constituent. It is used topically to treat open infections such as infected eczema and infected dermal ulcers, and as a prophylaxis in operative wounds[13]. Bacitracin binds to C55-isoprenyl pyrophosphate, a biphosphate lipid transport molecule that carries the building blocks of the peptidoglycan bacterial cell wall[14]. The binding interferes with the enzymatic dephosphorylation of the C55-isoprenyl pyrophosphate and prevents peptidoglycan synthesis, thereby inhibiting bacterial cell growth.

Mupirocin

A natural crotonic acid derivative extracted from a strain of Pseudomonas fluorescens. It has shown excellent activity against gram-positive staphylococci and streptococci. It inhibits bacterial protein synthesis by specific reversible binding to bacterial isoleucyltRNAsynthase[15]. It has excellent activity against gram-positive staphylococci and streptococci. It is used primarily for the treatment of primary and secondary skin disorders, nasal infections, and wound healing.

Dapsone

A sulfone synthesized in 1908 was initially used as an antileprosy agent[16]. It is well known for its powerful antiinflammatory effects in addition to its antimicrobial abilities, it was frequently used for severe inflammatory forms of acne before the advent of systemic retinoids but was limited by systemic toxicity. Recently, a 5% topical gel formulation has been approved for the treatment of mild-to-moderate acne[17]. Early studies suggest that the topical formulation is safe and that monitoring for hemolyticanemia is not necessary, even among these with known glucose 6-phosphate dehydrogenase deficiency. Although it is in the sulfa family, it appears that dapsone may not be very effective against the bacteria that are commonly treated with topical agents. In one study, the minimum inhibitory concentration (MIC) for dapsone was measured for S. pyogenes, S. aureus, and E coli, and found to have essentially no antibacterial effects against these pathogens[18]. Despite these negative findings, it is possible that other uses for topical dapsone will be uncovered as it becomes more widely available.

Retapamulin

It belongs to a class of the naturally occurring pleuromutilin produced by Pleurotusmutilus, an edible mushroom. The pleuromutilin class has a unique mode of action, which involves inhibition of bacterial protein synthesis by binding to the prokaryotic ribosome. Retapamulin selectively inhibits bacterial protein synthesis through an interaction at a binding site on the 50S subunit of the bacterial ribosome that differs from that of other antibiotics[19]. Retapamulin is predominantly bacteriostatic against Staphylococcus aureus and Streptococcus pyogenes. It is used primarily for the treatment of primary skin infections, and secondarily infected lesions.[20]

Erythromycin

Topical erythromycin is used most frequently in the treatment of acne vulgaris; however, an ointment formulation is also useful in postsurgical wound care. Erythromycin is a macrolide antibiotic that is derived from Streptomyces erythraeus. It is a bactericidal drug against gram positive bacteria, which works by irreversibly binding to the 50s subunit of the bacterial ribosome, thereby inhibiting protein synthesis[21]. Because of the expensive of other topical antibiotics and the potential for sensitization, erythromycin 2% powder was compounded in white petrolatum to form erythromycin 2% ointment. This ointment proved to have a very low incidence of sensitization at 0.022% in surgical procedures. In addition, the rate of wound infection was 0.586%. Erythromycin 2% ointment was therefore deemed to be a worthy substitute for other topical antibiotics.

Gentamicin

It belongs to the aminoglycoside group of antibiotics. It is a product of a strain of Micromonosporapurpurea[22]. The mechanism of action of gentamicin appears to be inhibition of protein synthesis and messenger ribonucleic acid translation. It has a similar “spectrum” to related antibiotics such as neomycin and kanamycin, but a rather greater activity than these against some species of bacteria. Almost all enterobacteria are sensitive to it, including species of Aerobacter, Escherichia, Klebsiella, Salmonella, Shigella, Proteus (three species fully sensitive, but P. vulgaris less so), and Pseudomonas[23]. A high degree of activity against Ps. aeruginosa is an outstanding property: Among Gram positive organisms the most sensitive are staphylococci. Streptococci (except S. faecalis) and pneumococci are also moderately sensitive, but much less so than to many other antibiotics. It is

bactericidal in concentrations little greater than those inhibiting growth. The application of a cream or ointment containing 0.1% gentamicin has been successful in the treatment of burns, bedsores, impetigo and other pyogenic skin infections, and of nasal carriers of staphylococci[24]. The principal indication for gentamicin is infection caused by Ps. aeruginosa, against which it is the most potent antibiotic known. Its activity against staphylococci, even when they are resistant to neomycin and kanamycin, is also important.

Polymyxin A and B

Polymyxins are decapeptides that are isolated from Bacillus polymyxa[25]. Because bacitracin is similarly isolated from Bacillus sp., there is potential for allergic cross-reactivity between polymyxin and bacitracin. However, cutaneous sensitization is rare, and systemic absorbance and toxicity are unlikely. The mechanism of action is to disrupt the phospholipid component of the cell membranes through a surfactant-like action, resulting in increased permeability of the bacterial cell[26]. They are bactericidal against some gram- negative bacteria, but their spectrum of activity is limited. Polymyxins are largely inactive against most gram-positive bacteria and Providencia. In contrast, polymyxins are bactericidal against P. aeruginosa, Proteus mirabilis, Serratiamarcescens, E. coli, Enterobacter, and Klebsiella. Combinations of polymyxin with zinc, bacitracin, and neomycin comprise some of the more common antibacterial ointments (i.e., Neosporin and Polysporin) and increase the spectrum of activity. Similar to the other topical antibiotics, polymyxins are indicated in prophylaxis and treatment of superficial wounds, in the treatment of secondary pyodermas, as adjunctive measures in burns, and for prophylaxis in the surgical wound. They are generally well tolerated and are most frequently used in combination with other topical antimicrobials for maximum efficacy.

Indolmycin

Topical indolmycin demonstrates good antistaphylococcal activity and seems promising for treating MRSA strains resistant to fusidic acid and mupirocin[27]. The agent is bacteriostatic but shows good in vitro activity against MSSA, MRSA, and vancomycin-intermediate S aureus (VISA), including strains resistant to mupirocin and fusidicacid[27]. Some indolmycin-resistant strains have emerged, with high-level resistance most commonly associated with an H43N mutation in tryptophanyl-tRNAsynthetase, the target enzyme of indolmycin[28].

Nadifloxacin

Nadifloxacin is a potent, broad-spectrum, qui- nolone agent approved for topical use in acne vul- garis and skin infections in Japan. Quinolones are bactericidal drugs that inhibit the bacterial DNA gyrase or the topoisomerase IV enzyme, two en- zymes absent in eukaryotic cells, thereby stopping DNA replication and transcription[29]. A European 12-week study comparing the clinical and bacte- riological efficacy of nadifloxacin 1% cream with erythromycin 2% cream has demonstrated that nadifloxacin was as efficacious and safe as eryth- romycin and that the number of nadifloxacin-re- sistant microorganisms was extremely low during the treatment period.

Rifalazil

Rifalazil and other benzoxazinorifamycins are modified rifamycins that contain a distinct planar benzoxazine ring[30]. Rifalazil shows high tissue penetration and achieves high intracellular levels.

Drugs within this family are promising as topical agents, but resistance has been a significant problem with rifampin, and the potential for development of resistance to topical forms deserves careful scrutiny.

Fusidic Acid

Fusidic acid belongs to the fusidanes, which have molecular structures similar to corticosteroids without the steroid-like effects[31]. It is derived from the fungus Fusidiumcoccineum that works by interfering with bacterial protein synthesis, by preventing the translocation of the elongation factor G (EF-G) from the ribosome. It is able to achieve a high penetration and concentration at the site of infection, and is highly effective against S. aureus. Many guidelines suggest fusidic acid as first line in the treatment of superficial skin infections and infected eczema, as the main bacterial culprit is S. aureus[32]. Topical fusidic acid and mupirocin appear to be equally effective in cases of primary cutaneous infections and scabies. Both ointments appear to be effective against Gram-positive, Gram-negative or a combination of these organisms. The only adverse effect was that of greasiness, which was higher in the mupirocin group. Randomized trials have demonstrated the existence of resistance to topical fucidin and oral fusidic acid. Recent studies from Yorkshire and Bristol have further highlighted this concern over growing fucidin resistance. The West Yorkshire study found that 50% of fusidic acid-resistant strains were from dermatology patients exposed to topical fucidin in the 6 months prior to the study. The Bristol study found a doubling of fusidic acid resistance in methicillin-susceptible S. aureus over a 4-year period.

There may be prolonged use of topical fucidin in people with actopic eczema. It is true that 90% of atopic eczema sufferers are colonized by S. aureus; however, the risk of atopic children developing MRSA infection in the future remains a growing and real concern. The resistance level to fucidin is low at present, most likely due to its unique molecular structure and therefore is less likely to share resistance mechanisms with other antibiotics. Prolonged treatment with fucidin ointment should be avoided, even in the community setting. Short-term use of fusidic acid, over a 2-week period, has not been found to increase resistance[33].

Neomycin sulphate

Neomycin is found in many topical medications such as creams, ointments, and eyedrops. The discovery of neomycin dates back to 1949. It was discovered in the lab of Selman Waksman. It is used to prevent or treat skin infections caused by bacteria.

Neomycin is an aminoglycoside antibiotic.Neomycin sulfate, the sulfate salt of neomycin B and C, is one of the most commonly used topical antibiotics[34]. The aminoglycosides are the compound containing characteristic amino sugars joined to a hexose nucleus in glycoside linkage. Neomycin (Sulphate) was derived from cultures of Streptomyces fradiae. Although bioavailability after oral administration is poor, neomycin is administer orally in patients with hepatic coma or portal-systemic encephalopathy[35]. Neomycin (Sulfate) is most often used topically as an antiinfective. Neomycin is not indicated for the treatment of systemic infections because it can cause irreversible ototoxicity. Neomycin was approved by the FDA in 1952. Neomycin is bactericidal in action and effective against gram-positive and gram-negative bacteria. Applying the medicine directly to the infected area allows the neomycin to act directly on the bacteria that are causing the infection. Its mechanism of action is to inhibit bacterial protein synthesis through irreversible binding to the ribosomal RNA, causing misreading of the bacterial genetic code of susceptible bacteria. Neomycin is actively transported into the bacterial cell where it binds to receptors present on the 30 S ribosomal subunit. This binding interferes with the initiation complex between the messenger RNA (mRNA) and the subunit. As a result, abnormal, nonfunctional proteins are formed due to misreading of the bacterial DNA. Eventually, susceptible bacteria die because of the lack of functional protein. This ultimately kills the bacteria and clears up the infection.

Chlorhexidine

Chlorhexidineis a cationic polybiguanide (bisbiguanide). It is used primarily as its salts (e.g., the dihydrochloride, diacetate and digluconate). Chlorhexidine is antibacterial agent and topical disinfectant. Chlorhexidine is active against vegetative bacterias and mycobecterias and has moderate activity against fungi and viruses and effective against gram-positive and gram-negative organisms, facultative anaerobes, aerobes, and yeast. At physiologic pH, chlorhexidine salts dissociate and release the positively charged chlorhexidinecation. The bactericidal effect is a result of the binding of this cationic molecule to negatively charged bacterial cell walls. At low concentrations of chlorhexidine, this results in a bacteriostatic effect; at high concentrations, membrane disruption results in cell death.

Chlorhexidinedigluconate (CHG) are cationic disinfectants widely used in aqueous personal products such as eye drops, lotions and creams. Chlorhexidine Acetate is a topical antiseptic, bactericide, strong function of broad-spectrum bacteriostasis, sterilization, used for disinfecting hands, skin, washing wounds and in gargles.

Newer Compounds

New antibiotics are being studied, including new topical macrolides, which belongs to a new family of macrolide antibiotics, shows excellent in vitro activity against propionibacteria, including erythromycin- and clindamycin-resistant propionibacteria.

Combination of topical Antibiotics

Most frequently used topical antibiotic agents contain compounds of several medications for more adequate antibacterial coverage. Neomycin, polymyxin B sulfate, and bacitracin zinc in combination (Neosporin) are considered active against S. aureus, Streptococcus pneumoniae, E. coli, Neisseria, and P. aeruginosa.30 However, the combination does not provide adequate coverage against Serratiamarcescens. Because of the neomycin component of this combination, caution must be exercised, as the potential for allergic sensitization does exist. Bacitracin zinc and polymyxin B sulfate are other commonly used compounds of topical antibiotics. They have a similarly extended spectrum of action but do not contain the neomycin component.

Introduction to excipients used in formulation of semisolid dosage form[36,37]

Pharmaceutical excipients or additives are used as inactive ingredients in dosage form. Additives are tool for designing dosage form. Additives are normally non drug derivative with no or little therapeutic

Table 1: Formulation Components

Component	Definition
Antioxidant	Prevents or slows oxidation of other components
Base	Major classes or types of formulation compositions based on composition and physical properties
Buffer	Acid-conjugate base mixture employed to control pH and therefore control ionization state of drug and impart stability
Chelating agent	Have the ability to bind metal ions; prevents auto-oxidation phenomena frequently catalyzed by metal ions and enhances action of preservatives by binding iron and copper ions essential to microbial growth
Emulsifying agent	Reduces surface tension of two phases in an emulsion, preventing coalescence of individual phases
Humectant	Promotes retention of water in a mixture
Permeation enhancer	Faciltates diffusion process of active ingredient across the stratum corneum by chemical modification
Preservative	Prevents or slows microbial growth; may be one of 4 major compound types: acid, alcohol, quaternary ammonium compounds, or organic mercurial
Thickening agent	Increase viscosity; may be natural, semi-synthetic, or synthetic

value but are useful in the formulation and development of the various pharmaceutical dosage forms.

Ideal properties of additives

- They must be non-toxic, non-irritating, inert
- They must be commercially available in acceptable grade
- They should be cheap, economic
- They must be physically and chemically stable by itself and in combination with drugs and other components

They must be compatible with drugs and other additives

Table 2: List of additives used in formulation of gel, ointment and cream.

S. N.	Additives	Ointment	Gel	Cream
1.	Form giver	• Oleaginous bases • Absorption bases • Emulsion bases • Water soluble bases	Geeling agent: tragacanth, methyl cellulose, HEC, HPC, HPMC, CMC, carbopols, pectin, gelatin, etc.	Cetyl alcohol, stearyl alcohol, methyl cellulose, acacia,tragacanth, xanthan gum, woolfat, waxes, etc.
2.	Solvent/bases/vehicles/ diluents		Glycerine, propylene glycol, glyceryl triacetate, sorbitol, etc.	Alcohol, glycerine
3.	Organoleptics	Perfumes- rose, jasmine, lily, sandlewood, cedar wood, etc		
4.	Formulation stabilizer (preservatives)	Methylparaben, propyl paraben, benzoicacid, benzylconiumchloride, etc. Antioxidants- butylated hydroxyanisole, propyl gallate, nor-dihydro guaireticacid, etc Chelating agent- maleic acid, phosphoric acid, citric acid, etc.	E.D.T.A	Methyl paraben, propyl paraben, chlorocresol, chloroform, quaternary ammonium compound, etc.

Classification of additives

1.Form givers

A number of additives used in formulation to give them physical form. Surfactant and hydrocolloids are two classes of additives that are used as form givers and form stabilizers

2. Solvent/bases/vehicles/diluents

They form the bulk of the formulation. Solvent are reffered to liquids which are used for formulation of ointments. These additives carries drug and also give bulk additives carries drug and also give bulk and influenze bioavailabilty.

3.Organoleptics :They make formulation acceptable to the human

4.Formulation stabilizer: These are antimicrobial agent maintain chemical stability of the formulation. They are known as preservative.

A **Evaluation parameters**

- pH
- Drug content
- Viscosity
- Spreadability
- Extrudability study
- Skin irritation studies
- *In vitro* release
- *In vivo* study
- Stability
- Consistency

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