Available online on 15.09.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

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Review Article

Pharmaceutical Skin Care: Skin Structure, Barrier Function, and Advanced Drug Delivery Modes

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Article Info:

Article History:

Received 19 June 2025
Reviewed 27 July 2025
Accepted 20 August 2025
Published 15 Sep 2025

Cite this article as:

Prajapati R, Vyas N, Luhana A, Solanki N, Patel RR, Patel H, Pharmaceutical Skin Care: Skin Structure, Barrier Function, and Advanced Drug Delivery Modes, Journal of Drug Delivery and Therapeutics. 2025; 15(9):175-193
DOI:
http://dx.doi.org/10.22270/jddt.v15i9.7364

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Abstract

The skin, as the largest organ of the human body, plays a vital role in protection, Thermoregulation, and sensory perception. It also serves as a complex and selective barrier to external agents, making it both a challenge and an opportunity for pharmaceutical interventions. This review provides a comprehensive overview of the skin's anatomy and physiology, highlighting the structural features of its three primary layers: the epidermis, dermis, and hypodermis. Special emphasis is placed on the stratum corneum, the outermost layer, which poses the main barrier to drug penetration. Understanding the skin's functional dynamics is essential for optimizing topical and transdermal drug delivery. The article explores conventional and advanced drug delivery systems utilized in dermatological and cosmetic formulations, including creams, ointments, gels, patches, liposomes, and nanoparticles. Recent advancements in nanotechnology and biocompatible carriers have enhanced drug solubility, stability, and targeted delivery, thereby minimizing systemic side effects while improving therapeutic outcomes. Additionally, techniques such as microneedles, iontophoresis, and sonophoresis are discussed for their potential in overcoming the skin barrier and delivering drugs effectively to deeper layers. This review also examines key factors that influence drug permeation, including molecular weight, lipophilicity, formulation pH, and skin condition. Regulatory considerations, formulation challenges, and patient compliance issues are addressed to provide a holistic view of pharmaceutical skin care. By integrating skin biology with novel drug delivery approaches, this article aims to inform the development of more effective, patient-friendly dermatological therapies and cosmeceutical products. Future directions emphasize personalized formulations, innovative delivery systems, and sustainable ingredients to meet the evolving needs of patients and the market.

Keywords: Skin, layers, Formulations, Drug delivery system

Introduction:

The skin, comprising the largest part of the body, constitutes about 15% of the total weight in adults. It fulfills essential roles, including shielding the body from physical, chemical, and biological harm, preventing excessive water loss, and facilitating the regulation. Furthermore, the body's mucous membranes are an integral component of the continuous skin.[1]

1) Structure of skin

Skin which made up by three layer A)epidermis B)dermis and C)subcutaneous fat tissues (hypo-dermis) listed from the outside in. Skin Structure which is shown in below Figure 1.1.

1.1. Layer of Epidermis: The epidermis serves as the body's initial defense mechanism against various external factors such as ultraviolet radiation, bacteria, and germs. This outer layer of skin is water- resistant and consists of around four to five closely packed sub layers of cells. One of the crucial functions of the epidermis is to facilitate the cycle of cell renewal. During this process, old and unhealthy skin cells are shed from the visible outermost layer called the stratum corneum, while new and healthy cells develop in the deeper sub layers of the epidermis. Additionally, the epidermis includes pores, which enable the elimination of oil and dirt from the body.[3]

A) The epidermis is the outermost layer of the skin and has several vital functions. Here are four primary functions of the epidermis.[4]

1) Hydration: The epidermis, specifically the outermost layer called the stratum corneum, plays a crucial role in retaining water and maintaining skin hydration. It acts as a barrier to prevent excessive water loss from the body, helping to keep the skin moisturized and healthy.

2) Production of new skin cells: The epidermis comprises a layer called the stratum basale, which is responsible for the continuous production of new skin cells. Cells within the stratum basale divide and migrate upward through the other epidermal layers. As they progress, they transform and eventually reach the outermost layer of the epidermis, where they are shed from the body, making way for the formation of new cells in the basal layer. This process ensures the constant renewal and rejuvenation of the skin.

3) Protection: The epidermis acts as a protective barrier for the body. It shields the underlying tissues and organs from external threats such as ultraviolet (UV) radiation, harmful chemicals, pathogens (bacteria, viruses, fungi, and parasites), and mechanical injuries. The epidermal cells are tightly packed together, forming a tough and resilient barrier that helps prevent the entry of harmful substances and microorganisms into the body.

4) Skin color: The epidermis contains specialized cells called melanocytes, which are responsible for producing a pigment called melanin. Melanin determines the color of the skin, hair, and eyes. The distribution and amount of melanin produced by melanocytes in the epidermis contribute to the variation in skin color among individuals. Melanin also provides protection against the harmful effects of UV radiation by absorbing and dissipating the energy from the sun's.

B) Sublayer of epidermis:

1) Stratum corneum (20-30 cell layers):

The skin's outermost barrier, the stratum corneum, protects internal physiological conditions and shields the skin from external harm. It is made up of corneocytes, which are created when epidermal Keratinocytes cells differentiate, and an inter-cellular lipid matrix that fills the spaces between the cornfield cells. The adhesive junctions known as corneodesmosomes, which connect corneocytes, give the stratum corneum its structural integrity. Desmoglein1 (Dsg1) and desmocollin1 (Dsc1), two trans membrane proteins from the adherence super family, make up the corneodesmosomes' intercellular attachments.[5] The stratum compactum and stratum disjunctum are among the approximately 15 flattened layers of corneocytes that compose the human stratum corneum. Positioned above the stratum compactum, the looser stratum disjunctum is responsible for the shedding of cells as it gradually loses its adhesive properties due to a decrease in inter-corneocyte adhesion. The stratum compactum, on the other hand, forms a deep and cohesive layer within the structure.[6]

2) Stratum lucidum (2-3 cell layers):

The outer layer of our skin, called the epidermis, has a thin and see-through layer of dead skin cells known as the stratum lucidum. This layer is made up of five layers of flat cells called Keratinocytes. These cells are filled with a substance called eleidin, which is an early form of a protein called keratin. Unlike other layers, the cells in the stratum lucidum don't have clear boundaries between them. When these cells release certain oily substances, it helps keep the skin moisturized. The thickness of the stratum lucidum depends on how quickly the skin cells divide. It is found above the outermost layer of the skin, called the stratum corneum, and below the layer called the stratum granulosum. Typically, it is found in areas of thick skin like the palms of the hands and soles of the feet.[7] The main job of the stratum lucidum is to reduce friction between the outermost layer of the skin and the layer beneath it.[8]

3) Stratum granulosam (3-5 cell layers):

Keratinocytes granules, present in the granular layer of the epidermis called the stratum granulosum, play a crucial role in maintaining the integrity and function of the skin. These granules are primarily composed of proteins rich in histidine and cysteine. Their main function is to bind and consolidate intermediate keratin filaments, which are structural proteins present in Keratinocytes. By binding the keratin filaments together, the keratohyalin granules help to strengthen the structure of the cells and promote the formation of a protective barrier. This barrier serves as a waterproof shield, preventing excessive fluid loss from the body and protecting it from external factors. In summary, the primary purpose of keratohyalin granules is to bind intermediate keratin filaments together,[9] thereby contributing to the formation of a waterproof barrier that prevents fluid loss and safeguards the body.[10]

4) Stratum spinosum (8-10 cell layers):

The stratum spinosum, also called the spinous layer or prickle cell layer, is a particular area in the epidermis found between the stratum granulosum and stratum basale. It consists of approximately 8 to 10 layers of cells. The cells in this layer, known as keratinocytes, are organized in a polyhedral structure and are connected to each other through desmosomes.[11]

5) Stratum basale:

The basal lamina, also known as the basement membrane, acts as a barrier between the stratum basale and the dermis. It is connected to the dermis through hemidesmosomes. Within this layer, there are actively dividing stem cells that range from cuboidal to columnar in shape. These stem cells continuously generate keratinocytes, which are responsible for producing keratin. Additionally, melanocytes can also be found in this layer.[12]

C) Several specialized cells can be found in the epidermis, including:

1) Keratinocytes cells:

Skin cells called keratinocytes produce and store keratin, a protein that gives skin its tensile strength. The primary epidermal cell type in the top layer of human skin, keratinocytes are crucial for the skin's defense against infection. In addition to serving as a physical barrier between the external environment and the body's interior, keratinocytes are crucial for anti-pathogen infection in the skin.[13]

Function: Keratinocytes' main function is to fortify the skin's defenses against harmful substances like heat, UV

rays, water loss, infectious bacteria, fungi, parasites, and viruses.[14,15]

2) Langerhans cells:

Langerhans cells ,which aid in infection prevention and immune system protection Langerhans cells populate the epidermis as a strong network of immunized sentinels from an early developmental stage. These cells act as the first line of defense for the cutaneous immune system against germs that enter the human body through the skin.[16]

Function: The immune cells T cells and B cells are immediately released when Langerhans cells identify a threat in the skin. Immune cells are in charge of snatching up invaders like bacteria and viruses as well as defending off wounds like cuts and scrapes.[17]

3) Melanocyte cells:

The pigment that determines the color of the skin, melanin, is produced by melanocyte cells. The term "melanocyte" refers to a number of cells found in the human body. Despite the fact that they are all neural crest cells (NCC), which are embryonic cells with the capacity to synthesize melanin, and that they are all found in each target site, their individual functions in each of these locations go far beyond simply producing melanin. Melanin, the pigment responsible for skin coloration, is synthesized within melanosomes by specialized cells known as melanocytes. These cells have a distinct dark and branching appearance. The melanocyte's main function is to produce melanin.[18] Melanocytes are derived from neural crest cells. They form a strong connection with keratinocytes in the human epidermis through their dendrites. The role of melanocytes in the pigmentation of the skin is well known.[19]

Function: Melanocytes produce the pigment melanin through a process known as "melanogenesis," which is present in the inner ear, nasal cavity, skin, hair, eyes, and skin. This melanogenesis produces pigmentation that lasts for a long time.

4) Squamous and basal cells Both basal and squamous cells have the potential to mutate, leading to basal cell carcinoma and squamous cell carcinoma, respectively.[2]

Squamous cells: Thin, flat cells that make up the epidermis' top layer [18]. These are flat cells found in the the top (outer) layer of the epidermis that are continuously shed as new ones develop. These cells can develop into squamous cell carcinoma, also referred to as squamous cell skin cancer.

Basal cells: The epidermis, the top layer of skin, is composed primarily of basal cells.Basal cells generate fresh skin cells. As new skin cells are produced, older skin cells gradually move closer to the skin's surface where they die and are shed off. A basal cell's DNA controls how many new skin cells are produced.[19]

1.2. layer of dermis:

The dermis is a layer of tissue composed of connective tissue situated between the epidermis and the subcutaneous tissue. The fibrous structure known as the dermis is made up of collagen, elastic tissue, as well as additional extracellular components like nerve endings, blood vessels, hair follicles, and glands. The dermis aids in sensation, Thermo-regulation, and support and defense of deeper layers of skin. Fibroblasts are the primary cellular components of the dermis, while histiocytes, adipocytes, mast cells, and other cell types also contribute significantly to the normal appearance and functioning of the dermis.[20]

Function:

- Preserving your skin's surface:
- Your blood vessels and the structure of your skin provide strength and flexibility to assist the preservation of your epidermis.
- Experiencing various sensations:
- The dermis is connected to nerve endings that allow you to pressure, discomfort, heat, cold, and a range of other feelings, such as itching.
- Sweating:
- During times of elevated body temperature or stress, the sweat glands located in the dermis secrete perspiration, which aids in the regulation of body temperature.
- Moisturizing your skin:
- The dermis of your skin contains sebaceous glands that release sebum, an oily lubricant that provides nourishment and a glossy appearance to your skin and hair
- Creating hair:

All of the skin on your body has hair follicles, with the exception of the soles of your feet and the palms of your hands.[21]

Dermis Layer:

1) Layer of Papillary: The uppermost layer of the dermis, called the papillary dermis, connects with the rete ridges of the epidermis. It is made up of collagen fibers that are small in size and arranged in an irregular manner. The connective tissue that makes up the papillary region is labile and areolar. Its papillae, or more specifically, dermal papillae, which extend towards the epidermis and either contain tactile Meissner's corpuscles or terminal networks of blood capillaries, give it its name.[22]

2) Layer of Reticular: The deepest layer of the skin, called the reticular dermis, offers structural support to the skin through its network of blood vessels and connective tissue. It also encompasses essential structures such as hair follicles, sweat glands, oil glands, and other related components.[23] The reticular layer gives the skin strength, structure, and elasticity because it is stronger than the papillary dermis.[24]

Dermis Cells:

1) Fibroblast: A specific type of cell called a fibroblast aids in the formation of connective tissue, a cellular material with a fibrous structure that connects and

supports other tissues and organs in the body. Fibroblasts are responsible for the production and secretion of collagen proteins, which contribute to the maintenance of the structural integrity of tissues and skeletal systems. They are crucial in the process of wound healing. Fibroblasts can be isolated from an individual through a straightforward skin biopsy and grown in a lab for use in genetic and other scientific research on that person.[25]

Function:

It performs a range of functions and acts as the building blocks for tissues and organs. This cell is responsible for maintaining the extracellular matrix (ECM) during periods of equilibrium. In response to stress, fibroblasts can adjust to their surroundings and communicate through localized signals. In response to injury, fibroblasts can transform phenotypes and synthesis the building blocks required to replace injured tissue.

Pathologic states, the extracellular matrix is produced in excess, and collagen is deposited in an uncontrolled manner, often resulting in irreversible organ dysfunction or a disfiguring appearance.[26]

2) Macrophages: **A** type of white blood cell known as a macrophage is part of the innate immune system and is responsible for digesting pathogens such as cancer cells, microorganisms, cellular debris, and foreign materials that lack proteins specific to healthy body cells.The mechanism that shields the host from harm and infection is known as phagocytosis. [27,28]

Function:

The three primary roles of macrophages in an inflammatory response are antigen presentation, phagocytosis, and immuno modulation via the production of different cytokines and growth factors. Inflammation is initiated, maintained, and resolved in large part by macrophages.[29]

3) Mast cells: A kind of white blood cell that may be found all throughout the body, but is most common in the lungs and intestines, close to blood and lymph veins, under the skin, and in nerves. Mast cells are essential for controlling different immunological responses as well as how the immune system functions. responds to certain parasites and germs. Among other things, they include histamine, heparin, cytokines, and growth factors. These substances are produced during some immune responses and allergy reactions. Numerous effects of these substances include angiogenesis and blood vessel expansion. During an allergic response, they may produce itching and flushing (a heated, red face). Additionally, they can result in severe low blood pressure, muscular discomfort, nausea, vomiting, diarrhea, and abdominal cramps.[30]

Function:

In the inflammatory process, mast cells are important players. Mast cells have the capacity to either slowly release inflammatory chemicals from storage granules or immediately release. when it is activated.Mast cells do not become active during allergic reactions until an allergen binds to IgE that is already coated on the cell.[31]

4) Schwann cells:

Schwann cells or neurolemmocytes are the main cells of the peripheral nervous system (PNS). Glial cells include those located at sensory nerve terminals like the Pacinian corpuscle, olfactory ensheathing cells, intestinal glia, and satellite cells. supporting PNS neurons. There are two classifications of Schwann cells: myelinating and nonmyelinating. Myelinating Schwann cells encase the axons of both motor and sensory neurons, creating the myelin sheath. In the human dystrophin gene, the Schwann cell promoter is situated in the downstream region, resulting in the production of shorter transcripts that are synthesized in a tissue-specific manner once again.[32]

Function:

The Schwann cell is crucial for the proper operation of the peripheral nervous system (PNS). Schwann cells are derived from neural crest cells and are divided into two types: myelinating and nonmyelinating cells. Both are essential for the maintenance and regeneration of neuron axons in the PNS.[33]

1.3 Hypodermis:

Skin's bottom layer are also called as hypodermis layer. The hypodermis, also known as subcutaneous tissue, insulates and protects the body, stores energy (fat), aids in temperature regulation, and connects the skin to muscles and bones. The hypodermis is one of three layers of skin in humans, the others being the epidermis (outer layer) and the dermis (middle layer). These layers, when combined, form a barrier against fluids, infection, and trauma.[34]

Functions:

Connection: muscles and bones are connected to dermis layer by the hypodermis.

Insulation: Your body's hypodermis produces perspiration to regulate your body's temperature and protect you from the heat. It also insulates against the cold.

Protecting your body: The presence of the hypodermis allows for the seamless mobility of the skin over the underlying tissues and muscles. Absence of the hypodermis would result in friction between the skin and these structures. Additionally, it acts as a protective cushion, safeguarding the organs, muscles, and bones.

Energy storing: The hypodermis is responsible for the producing adipocytes, which are fat cells that store energy.[35]

2) Antifungal activity:

A fungus-related skin condition called mycosis is referred to as a fungal infection.There are many kinds of fungal infections The earth, plants, and even your skin can contain them. In certain cases, they might result in rashes or other skin issues.[36]

2.1 Classification of fungal infection or mycoses:

Fungal infection are based on three factors: (1) infected site (2) the pathogen's mode of acquisition, and (3) the fungus's type of virulence.

1) On Infected site:Fungal infections, known as mycoses, can be classified into various types based on the degree of tissue involvement and the host's immune response. These types include superficial, cutaneous, subcutaneous, and systemic (deep) infections, and the classification is determined by the specific characteristics of the infection and the way the host's body reacts to the pathogen.

The pathogen's mode of acquisition:

2) The pathogen's mode of acquisition: Infection-causing fungi can be either internal or external. External fungus can enter the body by a subcutaneous pathway, the skin, or the air. Internally generated infection can take the form of colonization by a member of the natural flora or the recurrence of an earlier infection.

3) The fungus's type of virulence: Primary pathogens may result in infections in healthy hosts. Pathogens that are opportunistic prompt disease in people with weakened host defence mechanisms.[37]

2.2.1. According to infected site:

A) Superficial fungal infection

Superficial fungal infections can be caused by a pathogen that has limited access to the stratum corneum and causes little or no tissue reaction. Superficial mycosis including the tinea versicolor, piedra, and tinea nigra;[38]

B) Cutaneous mycoses:

Skin, hair, and nails types of fungal infections are known as cutaneous infections. These fungal infections can be brought on by yeast (Candida species), nondermatophyte fungi, or dermatophytes most frequently.A fungus that causes tinea, a fungal infection, is referred to as a dermatophyte. Hence, dermatophytoses are referred to as tinea infections and are further classified depending on the specific area of the body that is affected, such as tinea pedis for the foot, tinea corporis for the body, tinea cruris for the groin, tinea capitis for the scalp, and tinea unguium for the nails. These are the most commonly encountered dermatophytic infections in the United States.[39] Yeast infections respond primarily to the azoles, whereas dermatophyte infections respond to griseofulvin, allylamines, and azoles. Treatment for nondermatophyte moulds can be more challenging and involve a combination of therapies.[40]

C) Subcutaneous mycoses:

Fungal infections known as subcutaneous mycoses primarily affect the dermis and subcutaneous tissue, with rare cases of systemic disease progression. These infections are typically found in tropical regions and typically result from the implantation of common organisms into the skin through local trauma. Immuno suppressed patients are at higher risk for these infections, just like other mycoses. Mycetoma, chromoblastomycosis, and sporotrichosis are the three main subcutaneous mycoses.[41]

Anti-inflammatory activity:

Anti-inflammatory medicines that minimizes inflammation in the body (redness, swelling, and pain). Anti-inflammatory medicines are prohibit the inflammation.[42] When your body encounters a pathogen (such as viruses, bacteria, or toxic chemicals) or undergoes damage, your immune system is triggered. The immune system deploys inflammatory cells and cytokines, which are substances that stimulate the production of more inflammatory cells, as its first line of defence.. These cells initiate an inflammatory reaction to engulf bacteria and other harmful substances or to initiate the healing process of damaged tissue. This can lead to symptoms such as pain, bruising, swelling, or redness. However, inflammation also affects internal bodily systems that may not be immediately visible.[43]

3.1 Inflammation types:

1) Acute inflammation

The acute inflammation happens in response to a number of circumstances where tissue damage may occur. Infection, reactions to hypersensitivity, chemical or physical agents, and necrosis of tissues are examples of common causes.[44] Resident immune cells, primarily consisting of resident macrophages, dendritic cells, histiocytes, Kupffer cells, and mast cells, initiate the process of acute inflammation in the affected tissue. These cells have the ability to recognize and bind specific molecules, known as pathogen- associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), through surface receptors called pattern recognition receptors (PRRs).PAMPs are substances that are linked to different pathogens but can be separated from host molecules. DAMPs are substances linked to cell damage and host-related injury.[45]

Features of acute inflammation: The loss of function, heat, discomfort, itching, and swelling are some of the symptoms of inflammation. Inflammation is a component of the body's intricate biological reaction to harmful substances like irritants, pathogens, and harmed cells.[46]

- Types of acute inflammation:Five distinct symptoms, known as the "cardinal signs," identify acute inflammation:[47]

1. Tumour (swelling)
2. Donor (pain)
3. calor (increased heat),
4. loss of function
5. Rubor(redness)

- Stages of acute inflammation

a. Injury response mechanism: When tissues are damaged due to infection, trauma, toxins, heat, or other causes, an inflammatory reaction, known as inflammation, takes place. Chemicals like

prostaglandins, bradykinin, and histamine are released by the damaged cells. These substances cause blood vessels to become permeable, leading to the leakage of fluid into the tissues and resulting in swelling.[48]

b. Inflammation phase

- Beginning right away after the injury, localized swelling is brought on by transudate, a fluid made up of water, salt, and protein that leaks from the injured blood vessels.[49]
- Inflammation regulates bleeding while preventing infection.
- The migration of repair and healing cells to the wound site is made possible by the fluid engorgement.
- During the inflammatory phase, bacteria, pathogens, and damaged cells are removed from the wound region.
- During this stage of wound healing, the presence of white blood cells, growth factors, nutrients, and enzymes leads to the characteristic swelling, heat, pain, and redness.
- Inflammation is a typical phase of wound healing; it only becomes problematic if it persists for an extended period of time or is severe.
- The inflammatory phase, which typically spans a few days, is characterized by homoeostasis, chemotaxis, and increased vascular permeability. This phase plays a crucial role in preventing further injury, closing the wound, eliminating cellular debris and bacteria, and facilitating cellular migration.[50]

C. Proliferative phase: The Proliferative Phase, the third stage of the healing process, initiates following the removal of debris from the wound. Its main objective is to fill and provide coverage for the wound.

The proliferative phase consists of three separate stages:

Wound filling, wound border contraction, and wound coverage (epithelialization) are the first three stages.

During the first stage, the wound bed is filled with connective tissue, resulting in the formation of glossy and deep red granulation tissue. Simultaneously, new blood vessels are generated. As the wound heals, the edges of the wound contract, causing them to shrink and be pulled towards the center.

In the third stage, the proliferation of epithelial cells initiates either from the wound bed or its edges, allowing them to traverse and ultimately cover the wound with epithelium. Typically, this proliferative phase lasts between four to 24 days.[51]

D. Remodeling and Strengthening phase:

Remodelling, the last step of healing, is when the granulation tissue transforms into a scar and gains increased tensile strength. The quantity of glycosaminoglycans, the water associated with the glycosaminoglycans (GAGs), and proteoglycans decrease as the granulation tissue matures, and the number of capillaries decreases due to capillary aggregation into bigger vessels. The granulation tissue loses metabolic activity and cell density throughout development. Collagen also undergoes type, amount, and organizational changes that improve tensile strength.[52]

The formation of the granulation tissue is finished before the Remodelling phase starts. As a result of mechanical strain and cytokines like TGF-, myofibroblasts may develop into smooth muscle actin (SMA) expressing myofibroblasts. After the healing process is finished, myofibroblasts undergo apoptosis. Collagen III, which is rapidly produced in the extracellular matrix (ECM), is gradually replaced by collagen I. Although collagen I has greater tensile strength, it takes a longer time to be deposited. Both the rate of blood flow and the development of new blood vessels decline. It develops an environment that is totally avuncular and acellular.[53]

Causes of acute inflammation:

1) Allergens,
2) toxic substances,
3) irritants, and
4) foreign bodies that are too large to be digested or harm macrophage phagosomes are some of the causes. Silica and asbestos are two examples of foreign bodies.[54]

2) Chronic inflammation:

Chronic inflammation, characterized as a prolonged and enduring inflammatory state, can last for months or even years. The severity and impact of chronic inflammation are influenced by the original source of injury or inflammation, as well as the body's ability to heal and reverse the damage.[55] Chroni inflammation can start even when there is no damage, and it often lasts longer than it should. Sometimes the cause of the inflammation's recurrence is unclear. Frequent recurrent infections, improper immune responses to healthy tissues, and health conditions like obesity can all play a role in contributing to chronic inflammation.[55]

4) Excipients

A medicine is made up of two main components: active pharmaceutical ingredient and excipient. Most, if not all, medicines would be impossible to manufacture without the use of excipients.[45] Excipients are ingredients that are added to medications to improve production, patient acceptability, stability, and release control, among other things.The majority of a drug product is typically made up of excipients, with very small amounts of the active molecule. . Excipients were previously referred to as inactive components.[46] Excipients are essential in the formulation of a dosage form. These are the ingredients that comprise the dosage forms, along with the Active Pharmaceutical Ingredients. explains all the different excipient types and sources, and also including their uses and how they can be applied to a **v**ariety of tasks. Excipients are best suited to a specific dosage form.[47] The

luminal fluids of the digestive system are an example of an aqueous environment where many active pharmaceutical ingredients (APIs) have poor solubility and sluggish dissolution rates. Specialized dosage forms can be developed to increase dissolution rate through a variety of processes, or excipients can be added to the formulation to aid in drug dissolution.[48] Excipients are substances present in dosage forms that do not serve as the active ingredient. As per the World Health Organization's definition, an active pharmaceutical ingredient (API) is a substance incorporated in a final pharmaceutical product that is intended to produce pharmacological effects or have an immediate impact on the diagnosis, cure, protection, treatment, or prevention of diseases, as well as to directly contribute to the recovery, correction, or improvement of health."[49] Pharmaceutical excipients are essential for absorption of drugs in the body. Excipients usually don't have any medicinal qualities. Its typical goal is to make the drug product manufacturing process easier and ultimately facilitate the drug's physiological absorption. The function of excipients in taste, disintegration, lubricity, flowability, and antimicrobial defence may be aided. A crucial step in the drug manufacturing process is choosing the right excipient to support the design of your pharmaceutical formulation.[50]

4.1 Role of excipients in the formulation of medicine:

Tablets, capsules, oral liquids, topical creams and gels, transdermal patches, injectable products, implants, eye products, nasal products, inhalers, and suppositories are among the numerous options available for administering medications. Pharmaceutical excipients, which are compounds added to pharmaceutical dosage forms, serve purposes beyond their direct therapeutic effects. These purposes may include aiding in manufacturing, providing protection, offering support, enhancing stability, improving patient acceptability, or increasing bioavailability. They might also help identify the product and improve its general usability or safety while being stored.[56]

4.2 Active pharmaceutical ingredient excipients :

Excipients are substances created to interact with active pharmaceutical ingredients (APIs) and improve their properties. Excipients are a useful tool for drug formulators because they can be made to promote a variety of ingredient qualities. They can be used to bulk up solid formulations that contain small amounts of APIs for long-term stabilization or to improve the activity of the active ingredient in the final dosage form, such as by facilitating drug absorption, lowering viscosity, or increasing solubility.[57]

5) Dosage form:

The term "dosage form" pertains to the actual formulation or delivery approach employed to create, manufacture, and provide a product for use. Examples of dosage forms include tablets, capsules, oral solutions, aerosols, ointments, inhalers, and suppositories. Each of these delivery methods utilizes distinct technologies or mechanisms to regulate, enhance, or direct the release, targeting, systemic absorption, or other aspects of drug delivery within the body.[58]

5.1. Types of dosage forms:

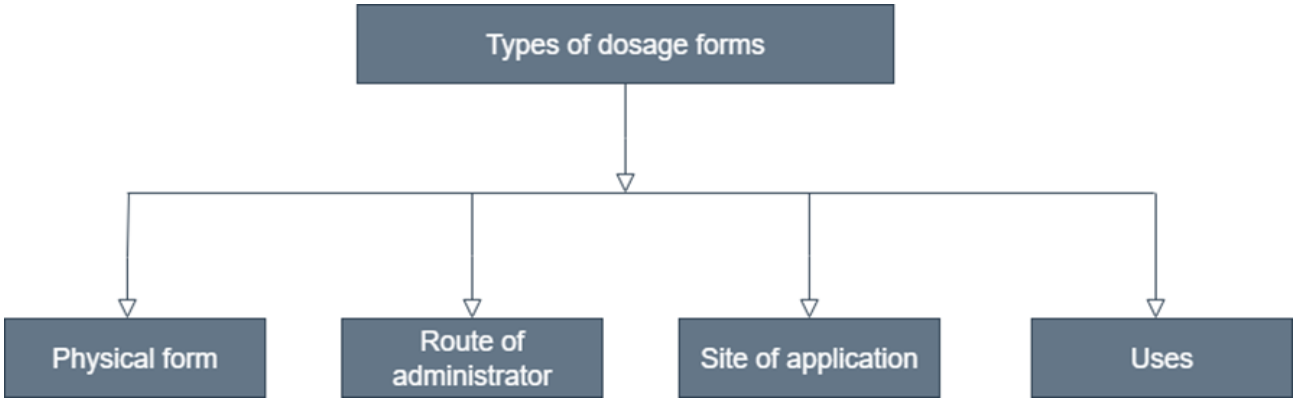

Figure 1.1: Types of dosage forms [5]

5.2. According to physical form:

5.2.1 Solid dosage forms:

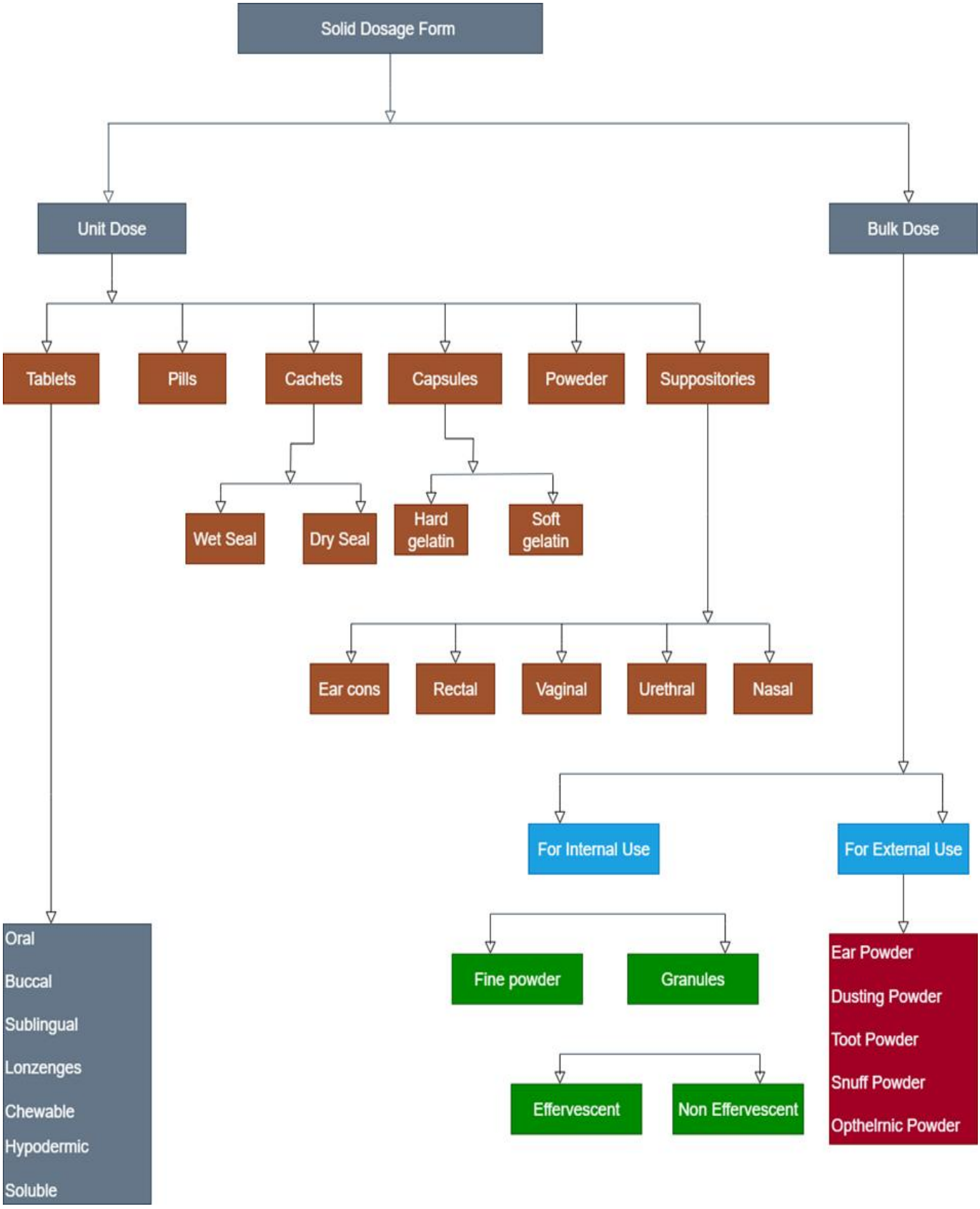

Figure 1.2: Classification of solid dosage forms [59]

5.2.2 Liquid dosage forms

5.2.2.1 Monophasic liquid dosage forms

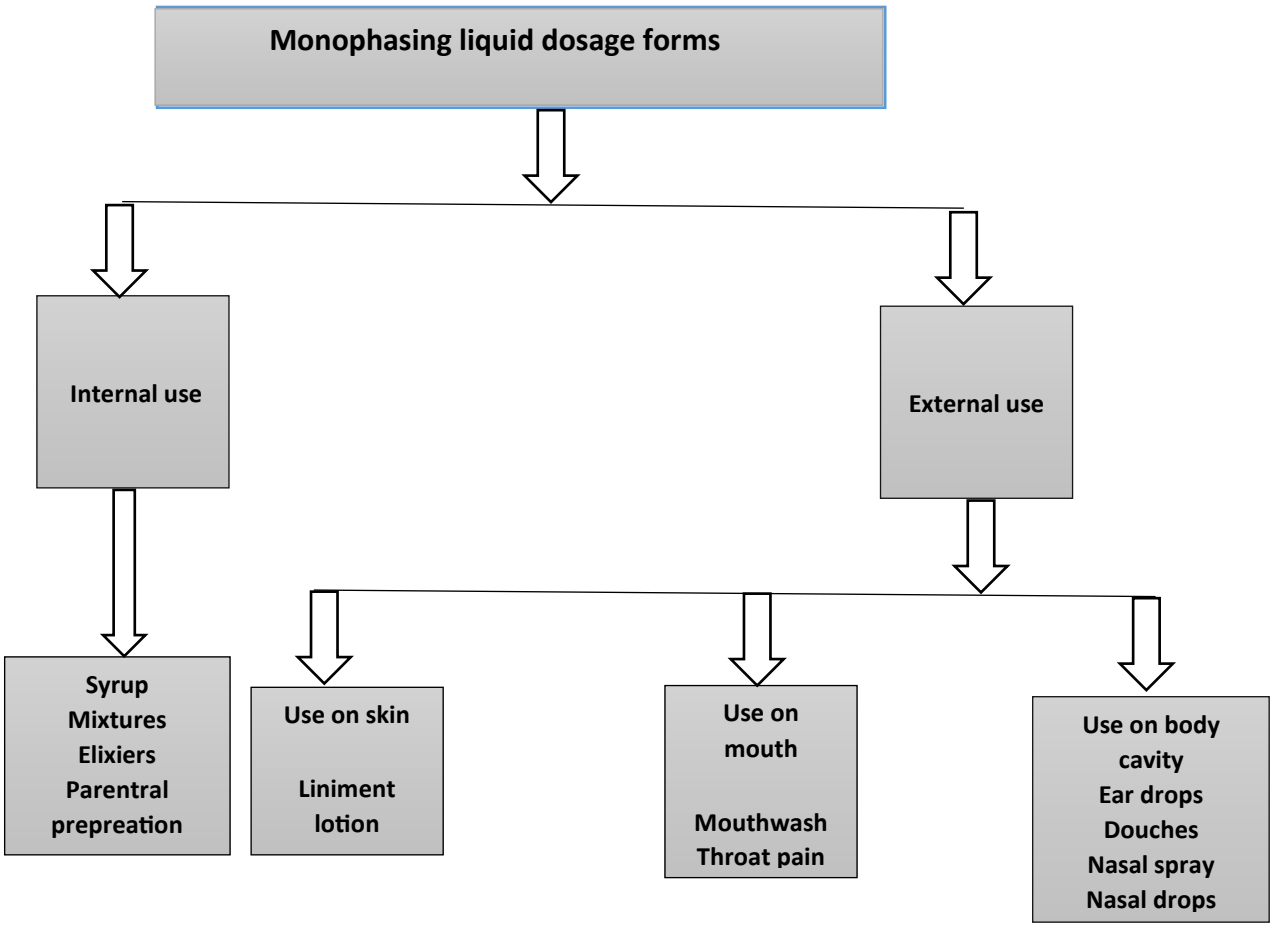

Figure 1.3: Classification of monophasic type of liquid dosage forms [60]

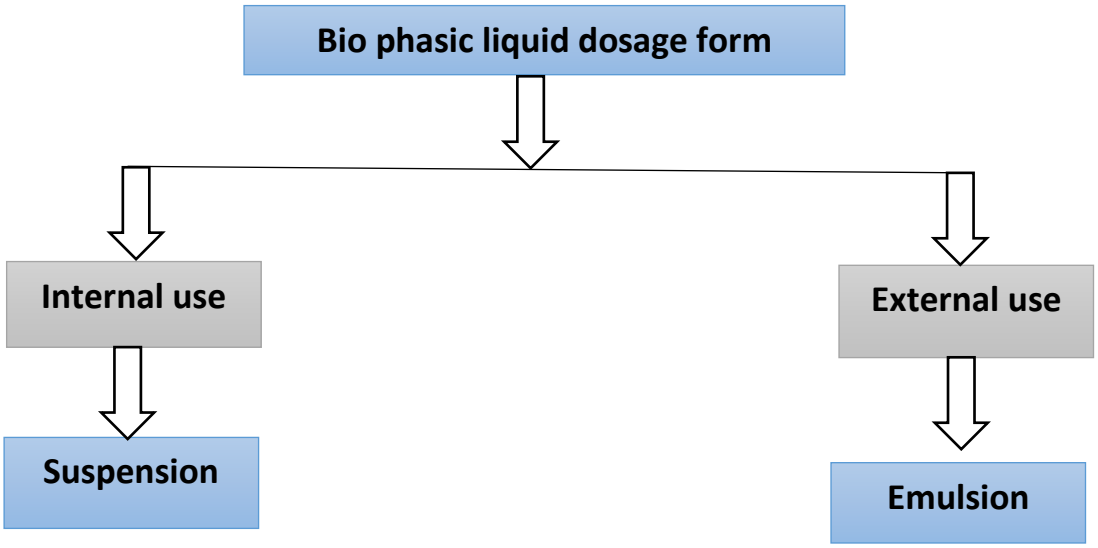

Figure 1.4: Classification of biphasic type of liquid dosage forms [61]

5.2.3. Semisolid dosage forms:

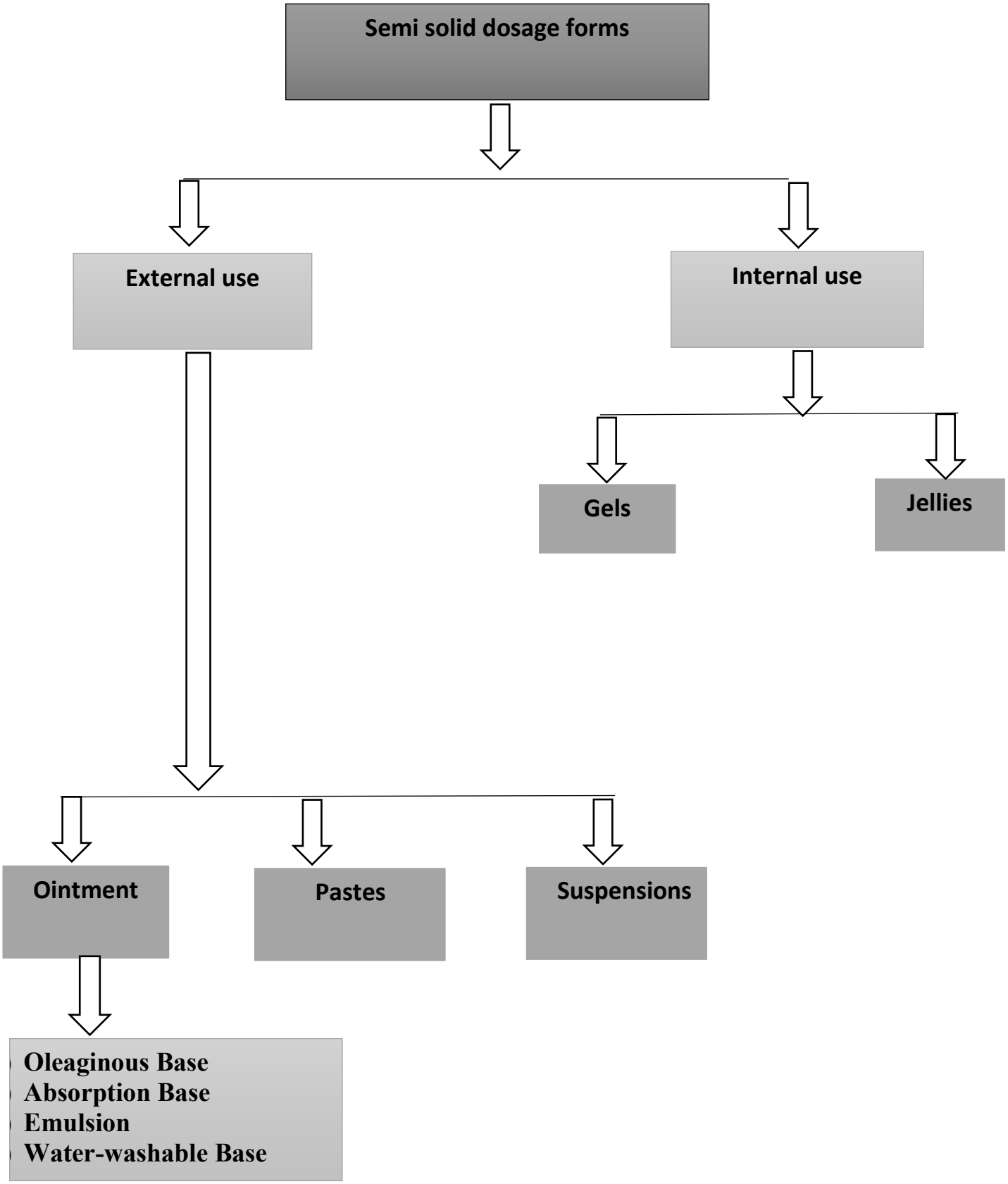

Figure 1.5: Classification of semisolid dosage forms [62]

5.2.4 Gaseous dosage forms:

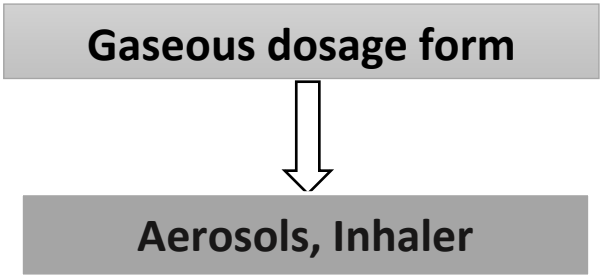

Figure 1.6: Classification of gaseous dosage forms [63]

5.3 According to uses:

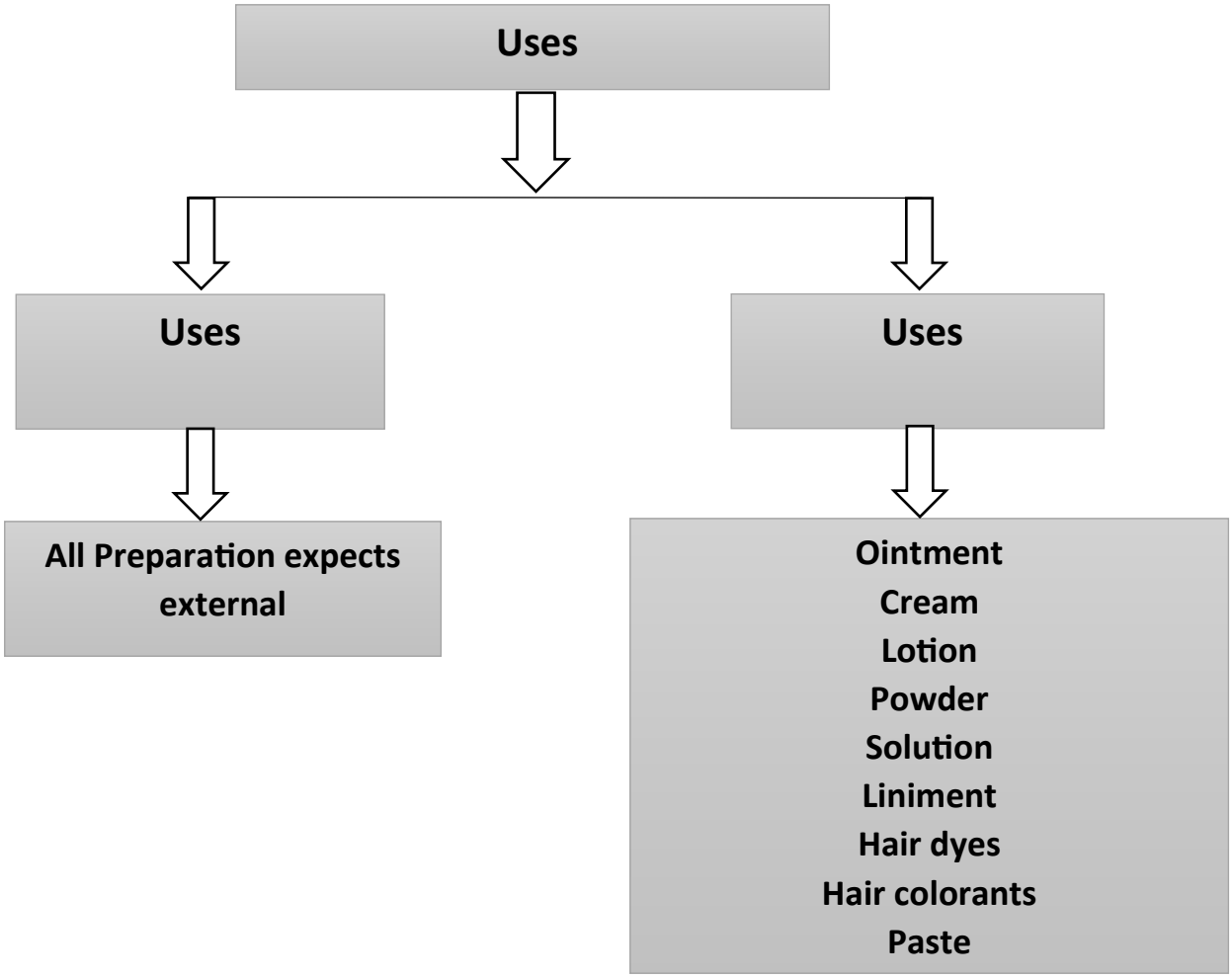

Figure 1.7: Classification According to use[64]

6 Ointment:

Ointments are a type of semisolid medication that, under shear stress, typically behaves like a viscoelastic material. They usually consist of medicinal components and are applied topically to the body to have a therapeutic effect. Numerous therapeutic materials that are applied topically to intact or damaged skin or mucous membranes come in semisolid forms that are variously referred to as ointments, creams, pastes, etc. It is primarily used as a skin protectant or emollient.[65]

Advantages of ointment:

- Compared to large liquid dosage forms, ointments are simpler to handle.
- Compared to liquid dosage forms, they are chemically stronger.
- They make it easier to apply the medication directly to the affected area of the body, protecting other parts from exposure to the drug.
- They are suitable for patients who have trouble taking medications orally or parenterally.
- They prolong the period of time the drug is in contact with the affected area.
- Since the liver is not involved, drugs applied as ointments have a higher bioavailability.[66]

Disadvantages of ointment:

- They have the following disadvantages over solid dosage forms:

✓ They are bulkier;

✓ It is challenging to determine the precise amount of ointment to apply to the affected area

✓ They are less stable.[67]

Ideal properties of ointment:

- It must be odorless, inert as well as smooth.
- Physically as well as chemically.
- It must be reconcilable with the skin.
- It should have a spreadable, softening consistency when applied to stressed skin.
- The wound's healing process shouldn't be slowed down.
- It shouldn't cause skin sensitivity or irritation.[68]

Types of ointment:

1. Unmediated ointment : These ointments do not contains any drugs. They are useful as emollients, Protect ants.[68]
2. Medicated ointment: Drugs with local or systemic effects are present in these ointments.

Sub types of mediated ointment:

a. Dermatological ointment: To treat skin conditions, topical dermatological agents are applied directly to the skin. Inactive creams and ointments are frequently utilized for regular skin care to uphold the health of the skin, especially if it is prone to skin disorders. They can also be utilized to administer medications for the prevention or treatment of skin disorders.[69]

b. **Epidermic ointment: A** topical cream with recombinant human epidermal growth factor (EGF) that may have anti-toxin properties against cutaneous side effects brought on by EGF receptor (EGFR/HER1) inhibitors. EGF locally activates Upon the topical application of EGF ointment, the EGF acts specifically in the area where it is applied, activating EGFR in the skin and reversing the inhibition of EGFR caused by systemic EGFR inhibitors. This might lessen the skin rash that EGFR antagonists cause. The tyrosine kinase EGFR is essential for preserving the integrity of the epidermis.[70]

c. Endothermic ointment: These ointments work as local irritants, emollients, stimulants in addition to releasing the medications that penetrate into the skin.[71]

a. Diadermicointment: These ointments are designed to release medications that penetrate the skin and have an impact throughout the body.[72]

Ophthalmic ointment: For some mild to severe eye conditions, an ophthalmic ointment is a semi-solid, greasy or creamy topical medication. Among many other eye conditions, ophthalmic ointments are frequently advised for eye infections, dry eyes, and blepharitis (inflammation of the eyelids).[73]

Uses: Eye infections are treated with this medication. Neomycin, bacitracin, and polymyxin are antibiotics found in this product that stop bacterial growth.Only bacterial eye infections are treated by this medication.[74]

Characteristics of ophthalmic ointment:

✓ Stability

✓ pH

✓ eye comfort

✓ preservation,

✓ sterility

✓ particle limitations[75]

Rectal ointment: Ointment is used to treat and relieve symptoms of anal fissures, as well as to help relieve pain and discomfort associated with haemorrhoids and haemorrhoidectomy.

Vaginal ointment An ointment for treating vaginal infections that is applied with a unique applicator is known as a vaginal ointment.[76-78]

Nasal ointment: When you sneeze or breathe through your nose, bacteria that can live there can spread to other people, so mupirozin nasal ointment is used to kill these bacteria. In particular, it is employed to eradicate the meticillin-resistant Staphylococcus aureus (MRSA) bacteria, which can result in skin infections.[79]

Uses: For the treatment of cold and allergy symptoms like runny nose, congestion, and sneezing, nasal sprays are frequently used. For instance, the flu can be treated with the oseltamivir drug found in Tamiflu nasal spray.[80]

Classification of ointment:

1. Hydrocarbon base (oleaginuous base)

Petroleum-derived hydrocarbons, also known as hydrocarbon bases, are oily or oleaginous bases. These bases are insoluble in water and anhydrous. These substances are used as occlusive dressings and for their emollient effects, which hydrate the skin.They are unable to hold or absorb water.[81]

- Petroleum (soft paraffin): Lubricating oil and a semi-solid hydrocarbon
- Yellow soft paraffin: made from petroleum, it can also include anti-oxidants like vitamin E and BHT. Range of melting: 38 to 56 °C
- White soft paraffin, type II, is made from petroleum. Range of melting: 38 to 56°C

- Hard paraffin is a mixture of solid hydrocarbons derived from petroleum in category III. 50 to 57 °C for solidification
- The liquid hydrocarbon mixture known as liquid paraffin is derived from petroleum.[82]

Example : Saturated and monounsaturated fatty acids are abundant in the oils of some oleaginous microorganisms, such as microalgae, yeast, fungi, and bacteria, whereas polyunsaturated fatty acids are abundant in thraustochytrids and microalgae.[83]

2. Absorption base:

An oleaginous composition that contains one or more emulsifiers and is capable of absorbing water to create a water-in-oil emulsion is known as an absorption base. It can be utilized as the entire or a portion of the oleaginous component of an emulsion appropriate for cosmetics, ointments, etc. Absorption bases may also be used as a component of the oleaginous material in O/W emulsions, although they are typically used in the preparation of W/O types of emulsions. Depending on the desired results, an absorption base may be used with or without the addition of additional emulsifiers or oleaginous materials.Various kinds of emulsions and ointments are prepared in the cosmetics industry using absorption bases.[84]

Advantages :

- **P**rotective, occlusive, and emollient properties of absorption bases are moderately good.
- They hold the incorporated medications in contact with the skin because they are difficult to wash off.
- They are liquid-absorbent.

a) Anhydrous absorption bases have a high capacity for water absorption and a moderate capacity for alcoholic solutions.

b) Emulsion absorption bases absorb varying amounts of water and/or alcohol because they already contain water.

Martindale's The Extra Pharmacopoeia states that the inclusion of suitable vegetable oils or petrolatum when combining wool-fat preparations leads to emollient creams with enhanced skin penetration and improved absorption. [85]

3. **Water removable base:** Are oil-in-water emulsions that can be washed off the skin or clothing with water. As a result, they are often referred to as "water-washable" ointment bases.[86]

1. **Water soluble base:** Water-soluble bases are frequently referred to as "grease less," completely water- washable, and do not contain any oleaginous components.Large amounts of aqueous solutions cannot be successfully incorporated into these bases because they soften significantly when water is added.A water-soluble base is an example of which is NF polyethylene glycol ointment.

6.1.2 Gels:

A gel is a semi-solid material that exhibits a broad spectrum of properties, varying from being soft and weak to hard. Gels are characterized as a cross-linked system with a notably low concentration, which remains motionless under steady-state conditions while enabling the diffusion of the liquid phase.[87] Semisolid preparations containing one or more medicines in a hydrophobic and hydrophilic base are known as pharmaceutical gels. Gels are created with appropriate gelling agents and may also include antioxidants, preservatives, and stabilizers. When applying gels to large open wounds or severely injured skin, the gel must be sterile.[88] Gels are created by chilling a colloidal solution or by a quick liquid-phase reaction with a high concentration of reagents. Gels are presently accessible in a diverse array of compositions, unlike liquids or ointments, gels possess the advantage of stability on the treated area and resistance to evaporation for an extended duration. This enables them to effectively achieve their intended purpose. For instance, certain gel formulations with muco adhesive properties can be employed in mucosal applications. Gel formulations are available for use as antimicrobials, anti-inflammatories, or anesthetics. Additionally, some formulations have been suggested to assist in wound healing or the control of bleeding after skin injuries.[89] Gels are a transparent, semisolid preparation designed for skin or mucous membrane application on the outside. Gels are semisolid materials made of large organic molecules or suspensions of small inorganic molecules in a liquid medium that take on a jelly-like appearance when a gelling agent is added.These are hydrophilic inorganic compounds or organic hydrocolloids.Tragacanth, Sodium Alginate, Pectin, Starch, Gelatin, Cellulose Derivatives, Carbomer, and PolyVinyl Alcohol Clays are all ingredients in them. These different gelling agents come in a variety of strengths.Microemulsions known as clear gels have dispersed phase globules with diameters between 10 and 60 nm. The thermodynamic stability of these emulsions is good. Since the disperse phase's globule diameter is less than the wavelength of light, microemulsions are transparent.[90] Gels are non-greasy, transparent or translucent semi- solid systems that are prepared by dispersing small or large molecules in an aqueous liquid medium that has been given a gelling agent's thickness.A single phase or a biphasic system can describe a gel.Jellies have a softer consistency than gels despite both being semisolid system dosage forms.[91]

Desirable properties of gels:

- ✓ Many gels exhibit thixotropy, whereby they liquefy under agitation and solidify under rest.
- ✓ Gels are typically materials that appear to be solid and jelly-like.
- ✓ It belongs to the non-Newtonian fluid category.
- ✓ Aerogels, renowned for their exceptional characteristics such as remarkably low density, elevated specific surface areas, and superb thermal insulation properties, can be produced by substituting the liquid with gas.

Hydration: An elastic gel that has completely lost all of its moisture can be renewed by adding water. A nonelastic gel won't gel if it is exposed to additional water after it has dried

- ✓ swelling: Elastic gels that have been partially dehydrated will swell as a result of absorbing water in the solvent. Swelling, a result of this, causes the gel's volume to increase.
- ✓ Syneresis: Many inorganic gels contract upon standing, and this contraction frequently results in solvent exudation. Syneresis is the name of this process.
- ✓ Thixotropy: Some gels are semisolid when at rest, but when disturbed, they turn into liquid sol. Thixotropy is the name given to this reversible sol-gel transformation. This property is present in iron oxide and silver oxide gels.[92]

Characteristic of gels:[93]

- ✓ This colloidal system has a liquid dispersed phase and a solid dispersion medium.
- ✓ It is a semi-solid that is immobile.
- ✓ It has a structure resembling a honeycomb.
- ✓ A lot of gels have a propensity to soak up liquid and swell.
- ✓ It can form without the need for such an agent.
- ✓ It falls under the categories of elastic gel and non-elastic gel.
- ✓ The Tyndall effect, Brownian motion, and electrophoresis are not visible in them.

Classification of gels

A) Based on colloidal phase

1. **Single phase system: organic (single phase); I**n single-phase gels, the liquid and dispersed macro molecules are seamlessly blended, with no discernible boundaries separating them. The macro molecules are evenly distributed throughout the liquid, creating a uniform composition [64] In the formation of single-phase gels, large organic molecules, also known as macro molecules, are uniformly distributed throughout a liquid. This results in a gel where there are no detectable boundaries between the dispersed macro molecules and the liquid phase. Natural gums (mucilages) or synthetic macro molecules can both be used to create single-phase gels.[94]
2. **Two phase system: inorganic (two phase);** Inorganic gels, such as aluminum hydroxide gel or bentonite magma, are often referred to as gels because they are made of floccules of tiny, distinct particles.

A) Based on the nature of the solvent:

1. Hydrogel:

Hydrogels, which are three-dimensional network structures, possess the capacity to absorb substantial quantities of water. The presence of either chemical or physical cross- links, as well as chain entanglements, typically prevents hydrogels from dissolving in water.[95] A hydrogel is a biphasic substance that contains at least 10% by weight or volume of interstitial fluid that is entirely or primarily composed of water, as well as porous, permeable solids. The porous permeable solid in hydrogels is a three-dimensional network of natural or synthetic polymers and a fluid that has absorbed a lot of water or biological fluids but is not water soluble.[96]

Properties of hydrogel: Hydrogels have gained significant popularity owing to their distinct properties, including high water content, softness, flexibility, and biocompatibility. The creation of hydrogels involves the physical or chemical cross-linking of hydrophilic polymers, which can be of natural or synthetic origin.[97]

Xerogel: Xerogels, a type of gel that solidifies, are formed by slow drying at room temperature without any restrictions on shrinkage. Xerogels are characterized by their higher porosity, larger surface area, and extremely small pore sizes. These gels are created using the sol- gel technique.[98]

Characteristics:[99]

- ✓ Nontoxic Cost-effective
- ✓ Biocompatible
- ✓ elevated surface area
- ✓ greater porosity
- ✓ readily modifiable

B) Based on rheological properties:

1. **Plastic gel:** For instance, a flocculated suspension of aluminium hydroxide, known as a Bingham body, demonstrates plastic flow. The rheogram plot illustrates the yield value of the gels, which represents the point at which the elastic gels deform and begin to flow.[100]
2. **Pseudo plastic gels:** Some non-Newtonian fluids have a property called thixotropy that causes their viscosity to change over time. The length of shear increases the viscosity of dilatant (shear- thickening) thixotropic fluids. Longer periods of shear result in lower viscosities for pseudoplastic (shear-thinning) thixotropic fluids. Numerous gels and colloids are pseudoplastic thixotropic materials; they take on a stable form when at rest but change to fluid state when disturbed due to a reversible gel-sol transformation phenomenon. The matrix relaxes and forms a solution with the characteristics of a liquid dosage form for ease of use when sheared by mixing, such as simple shaking. Thixotropic fluids exhibit increasing flow and thinning as the duration of mixing increases, even at the same rate of shear as

pseudoplastic fluids do.[101]

3. **Thixotropic gels:** Thixotropy is the reversible behavior of some gels, which cause them to liquefy when shaken, stirred, or otherwise disturbed and to reset once left to stand. Paint exhibits thixotropy, such as lithopone in oil, which, when stirred, flows freely but transforms into a gel-like state when left standing.[102] In liquid pharmaceutical preparations, thixotropy is a favorable property. A well-prepared thixotropic suspension, when subjected to shaking, remains suspended in the container without settling quickly. With increased shaking time, the suspension becomes more fluid, resulting in a greater reduction in viscosity or an increase in flow. For intramuscular depot therapy, a similar pattern of behavior is preferred for parenteral suspensions, emulsions, lotions, creams, and ointments. The amount of thixotropy and the rate of sedimentation both affect how stable a suspension is; the more thixotropy, the slower the rate of settling. It's significant to note hat a system's degree of thixotropy may change over time (such as during storage during shelf life) and lead to an ineffective formulation.[103]

A) Based on physical nature

1. **Elastic gels:** These are the gels that have the elasticity quality. They easily alter their shape when force is applied, then quickly return to their original shape when the force is released. Examples of this include gelatin, agar-agar, starch, etc.[104]

2. **Rigid gels:** For the purpose of "washing" or removing attachments, rigid gels are a controlled way to apply moisture locally or all over an object. These conservator can modify the ratio of gellan gum to water to alter the amount of moisture introduced.[105] These are the gels that lack the property of elasticity, meaning that when they become rigid from dehydration they cannot return to their original state through water heating. They don't display the imbibitions phenomenon. Silica acid is the best illustration of these gels.[106]

Characteristic of rigid gels:[93]

- ✓ When heated (dehydrated), they produce powder.
- ✓ Powder cannot be made into the original gel by adding liquid or water.
- ✓ They cannot be reversed.
- ✓ They fear lynxes.
- ✓ They don't exhibit intoxication.
- ✓ Non-elastic gels are those made of inorganic substances.

Serum:

A composition with a lot of active components is called a serum. One or more specific concerns may be the focus of a serum. A serum does not include as many components as a moisturizer or cleanser. Instead, it offers stronger actives that penetrate the skin more effectively and profoundly.[107] A highly concentrated preparation, serum can be made from water or oil like any other cream. A serum has a small number of components that are intended to maximize the availability of the active substance, which might be a vitamin, growth factor, botanical extract, etc. Because serum has a thinner viscosity, they not only absorb fast but also reach the deepest layers of the skin to target different parts and provide optimum efficacy.[108] Because of their potent effects and very few adverse effects compared to those of synthetic medications, herbal formulations have consistently attracted significant attention.[109]

Types of serum

1) Hydrating serum:

HA serums absorb into the skin and function to moisturize from within the layers of the skin by drawing in water almost like a sponge, in contrast to other moisturizers that tend to sit on top of the skin. This means that moisturizing serums can maintain healthy skin and soften fine wrinkles on the skin's surface.[110]

2) Anti-aging serum:

With the aim of enhancing the appearance of your skin, serums that assist elegant aging are skin care products that contain active ingredients that target the outward indications of aging, such as fine lines, wrinkles, and age spots.[111]

3) Exfoliating serum:

Severe lack of moisture, fine lines, wrinkles as well as hyperpigmentation, exfoliating serums are the most effective choice. An exfoliating serum's acids will aid in removing dead skin cells and battling skin issues like discoloration, dark spots, and early indications of aging.[112]

4) **Firming serum**

An anti-aging innovation in skin structure and contour is called as Firming Serum. A more defined face contour can be achieved with the help of Firming Serum, which is specifically made to noticeably tighten and firm the skin.[113]

5) Brightening serum

A skin-brightening serum is a cosmetic item containing potent ingredients intended to significantly lessen dullness and discolouration. They are occasionally referred to as skin lightening or skin brightening (not skin whitening) products.[114]

Transdermal drug delivery system:

The transdermal drug delivery system (TDDS) is a controlled drug delivery method that seeks to administer medication through the skin at a predetermined and controlled rate. This approach offers advantages such as prolonged therapeutic impact, reduced side effects, increased bioavailability, improved patient compliance, and ease of discontinuing drug therapy.The stratum corneum is believed to be the rate-limiting barrier in transdermal penetration for the majority of molecules. For most molecules, the stratum corneum is thought to

be the rate-limiting barrier in transdermal permeation. Appendageal, transcellular, and intercellular routes are the three primary routes by which drugs can enter cells.[115] approximately 74% of medications taken today are taken orally and are not as effective as desired. Transdermal drug delivery systems were developed to enhance such characters. Transdermal drug delivery is the process of administering drugs through the skin to produce a systemic effect, in contrast to traditional topical drug delivery methods. Transdermal drug delivery systems (TDDS) are specific formulations where a significant portion of the drug is transported into the systemic blood circulation, while the remaining portion is targeted to viable epidermal and/or dermal tissues of the skin for localized therapeutic benefits. The safety, effectiveness, and quality of the transdermal drug delivery system depend greatly on the adhesive. Topical therapeutic agent administration has many benefits over traditional oral medicaments.[116]

Topical drug delivery system

A drug's clinical effectiveness when applied topically is influenced by both the drug's accessibility to the target site and its pharmacologic characteristics. The majority of drugs intended sites of action used to treat dermatological conditions is located within the living tissue of the skin. The skin topmost layer are thin and that is known as stratum corneum, it is important impediment for drug delivery by dermal. Clinical drug usefulness is frequently constrained by its inability to cross the stratum corneum, which it needs to reach its target site. [117] The benefits of topical drug delivery include ease of administration, a compliant patient, increased compliance, and eliminating first-pass metabolism. lower rates of absorption and cosmetic considerations are disadvantages.[118]

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