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An Exploration of Features of Excipient Selection in the Formulation of Semi-Solid Dosage Forms: A Comprehensive Review

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Abstract

In the domain of pharmaceutical formulation, the selection of excipients for semi-solid dosage forms stands as a pivotal aspect, influencing the product's efficacy, stability, and patient acceptability. Therefore the formulation of semi-solid dosage forms demands meticulous consideration of excipient selection to achieve desired product characteristics and therapeutic outcomes. This comprehensive review embarks into the multifaceted landscape of excipient selection in semi-solid formulations, elucidating key features and considerations critical for formulation development. An excipient interacts with the drug in the dosage form and/or provides a matrix that affects critical quality attributes of the drug, including solubility, stability and bioavailability. Through a systematic exploration, various excipients including gelling agents, emulsifiers, viscosity modifiers, and preservatives are examined for their roles in imparting desired rheological properties, stability, skin compatibility, and drug release kinetics. Limited understanding of excipient functionality can compromise product quality and process control. "Safety and efficacy": Excipients can be associated with adverse events, either by direct action or by developing undesirable adducts. Additionally, advancements in excipient technology, regulatory considerations, and strategies for excipient compatibility assessment are discussed. By synthesizing insights from current literature and industry practices, this review serves as a valuable resource for formulation scientists, researchers, and regulatory authorities engaged in the development and optimization of semi-solid dosage forms.

Keywords: *Creams, Excipients, Gels, Ointments, Pastes, Semi solids*

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1. Introduction

The International Pharmaceutical Excipients Council (IPEC) defines an excipient as any substance other than the active medicament or prodrug that's involved in the manufacturing process or is contained in a finished medicinal dosage form (The International Pharmaceutical Excipient Council, 2014). Nonactive medicinal excipients are chemicals with a wide range of molecular sizes, from small molecules to large polymers, and a large variety of unique physicochemical characteristics. Thus, pharmaceutical excipients offer a wide range of properties to impact numerous characteristics of a pharmaceutical product, thereby achieving the optimal remedial efficacy. The overall distribution of excipients in dosage form designing can be better appreciated from the fact that more than 70% of the formulations contain excipients at a range more than the drug. In reality, no single excipient would meet all the criteria; thus, a concession of the different conditions has to be made. For example, although extensively used in pharmaceutical tablet and capsule formulations as a diluent, lactose may not be suitable for people who are deficient of the intestinal enzyme lactase to break down the sugar, which leads to the gastrointestinal tract symptoms similar as cramps and diarrhoea. Excipients are not inactive and have substantial impact on the manufacture and quality, safety, and efficacy of the drug substance(s) in a dosage form. Further, variability in the performance of an excipient is a crucial determinant of dosage form performance.

The role of excipients varies depending on the individual dosage form. These include

- Regulating solubility and bioavailability of the drug
- Increasing stability of the drug in its dosage forms
- Promoting drug to hold a suitable polymorphic form
- Continuing pH and osmolarity of liquid products
- Acting as antioxidants, suspending agent, emulsifier, aerosol propellants, base, tablet diluent
- Averting aggregation or dissociation
- Modulating the immunogenic response of drug (e.g., adjuvants) and various others. In these various context, excipients and issues related with them can be considered in the following different areas.

Processability: Good understanding of the characteristics and functional contributions of excipients aid in the day-to-day manufacture of a dosage form. In addition to their functional performance, excipients should be chemically stable, nonreactive with the medicine and other excipients, inert in the human body, have low equipment and process sensitivity, have pleasing organoleptic properties, and are well characterized and well accepted by the manufacturers and nonsupervisory agencies. Nearly 800 excipients are presently used in the marketed pharmaceutical products and this number is anticipated to grow with new therapeutic categories, such as gene therapy and cell therapy, and new drug delivery technologies.

1.1. Semi Solid Dosage Forms

Semi-solid dosage (SSD) forms are a type of medications which are neither solid nor liquid in phases, they are nearly in between these two phases. These medications are applied to the skin, nasal mucosa, cornea, rectal or vaginal tissue (mostly via suppository), buccal tissue, ear, or urethral membrane.

They contain one or more active ingredient dissolved or uniformly dispersed in a suitable base and any suitable excipients such as emulsifiers, viscosity increasing agent, antimicrobial agent, and stabilizing agent (Idson and Lazarus, 1991). SSD forms mostly involve two phases: oil and water. One phase is continuous, or external, while the other phase is dispersed, or internal. Active constituents can be dissolved in one or both phases.

Pharmaceutical semisolid dosage preparations include ointments, pastes, cream, gels, etc. A wide range of raw requirements is available for the preparation of a semisolid dosage form. In addition to conventional medicinal components like preservatives, antioxidants, and solubilizes, the initial ingredients of a semisolid dosage form are distinctive and essential to its formulation. The choice of suitable raw materials for a expression development is made on the base of the drug delivery conditions and the particular need to provide sufficient

emolliency or other quasi-medicinal characters in the preparation. Generally, semisolid dosage forms are in combined forms.

Semisolids are distributed in a wide range of dosage forms, each having unique properties (Table 1).

Advantages of semi-solid dosage forms:

- It is used external.
- Suitable dosage form for bitter drugs.
- More stable than a liquid dosage form.
- First pass metabolism is avoided.
- Original action and point specific action of the drug on the affected area.
- Accessible for unconscious patient.

Disadvantages of semi-solid dosage forms:

- May cause staining.
- The accuracy cannot be measured for the semisolid dosage form.
- Application with a finger may cause contamination.
- May cause irritation or allergy to some patients.
- Physio-chemical is less stable than a solid dosage form.
- Large sized drug particles are not absorbed so easily into the skin.

Table 1: Ideal Properties of Semi-Solid Dosage Forms (Blaug and Ahsan, 1961)

Physical Properties	Physiological Properties	Application Properties	Storage Properties
a. Smooth texture b. Elegant in appearance c. Non-dehydrating d. Non-greasy and non- staining e. Non-hygroscopic	a. Non-irritating b. Do not alter membrane function c. Miscible with skin secretion	a. Easy applicable with efficient drug release b. High aqueous washability	a. Not exceed 25^{o} degrees b. Stored in a well closed container c. Not be allowed to freeze

1.2. Ideal Properties of Semi-Solid Dosage Forms

1.3. Classification of Semi Solid Dosage Form

Ointments: Ointment is a viscous semisolid preparation used topically on a variety of body surfaces. These include the skin and the mucous membrane of the eye, vagina, anus, and nose. The ointment should be of similar consistency that can fluently rubbed on the skin. An ointment act as a emollient in nature to make a skin more pliable. Medicated ointment primarily corresponds with a drug and a vehicle is called as a base. The vehicle is used as a skin defensive and emollient. The ointment in earlier time were semisolid preparation with medicament dispersed uniformly in a adipose base; while the ointment being prepared at the present time do not contain any oleaginous substance.

Gels: Gels are semisolid preparation proposed for use on the skin or the mucous membrane. This is a semi-rigid structure in which the movement of dispersing medium in dispersed phase is limited by an interweaving three-dimensional system of particles (Jain, 2006). Vast volume of watery or hydro alcoholic fluid are entangled in a system of colloidal solid particles which may comprise of organic polymers from synthetic or natural origin or Inorganic substances.

Creams and Lotions: Creams are semisolid dosage forms consists of more than 20% water or volatile components

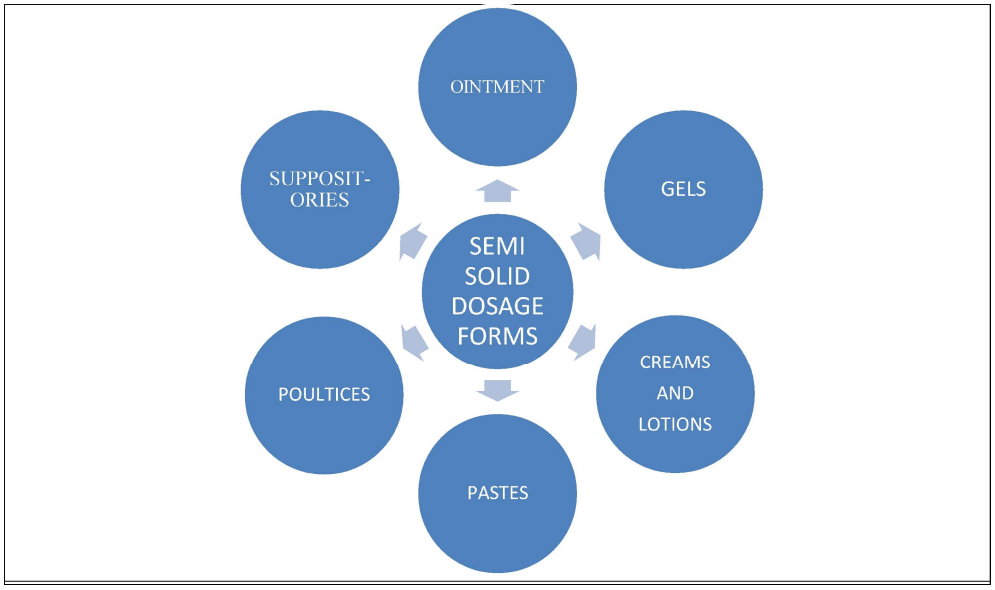

Figure 1: Classification of Semi Solid Dosage Form

and typically lower than 50% hydrocarbons, waxes, or polyols as vehicles. They also consist of one or more medicaments which are dispersed together to form a suitable cream base.

Lotions: A semi solid forms, generally aqueous or occasionally alcoholic preparation containing insoluble material intended for external operation without rubbing, in such skin conditions as itching, infection, allergy, pain, or the like.

Paste: Paste is an introductory pharmaceutical semi solid form. It contains a fatty base (e.g., petroleum jelly) and with at least 25% of a solid compounds (e.g., zinc oxide). Pharmaceutical pastes are generally intended for external application to the skin. They are generally present in thickened and not easily melt at physiologic temperatures. Pastes are applied externally on the surface of the skin, in order to give a defensive covering. They contain high powder content which provides a stiff and thick consistency to the formulation and also make them porous, which allows perspiration through it. The major difference between a paste and an ointment is that the former are stiffer and low slithery. They are generally prepared by dissolving the active medicament in different base.

Poultices: Poultices are semisolid dosage forms intended to applied to externally its soft, thick wet masses of solid substances to the skin for their fomentation action in order to give relief from pain or relieve inflammation or to act as counter-inconvenience. It consists of a hydrophilic heat-retentive base in which solids or liquids are dispersed. They are generally spread thickly on a suitable dressing and heated before application to the skin (Mehta, 1997).

Suppositories: A Suppository is a semisolid dosage form used to deliver medications by insertion into a body perforation where it dissolves or melts to exert local or systemic effects (Remington, 2012). There are three types of suppositories, each to insert into a different sections: rectal suppositories into the rectum, vaginal suppositories into the vagina, and urethral suppositories into the urethra of males (Aulton and Taylor, 2013). This term derives from the Latin suppositus, meaning "to place under."Suppositories are ideal for infants, older individuals and post-operative patients, who are unable to swallow oral medications, and for individuals facing severe nausea and/or vomiting (Ansel *et al.*, 2017).

1.3.1. Ointments

Ointments are semi-solid dosage forms that are designed for external use. They are typically made with a combination of oil and water, as well as other constituents like pharmaceutical-grade waxes, emulsifiers, and preservatives. Ointments are normally thicker in nature than creams and lotions, which makes them ideal for treating conditions like eczema.

Figure 2: Ointment

Hydrocarbon or oleaginous bases: Oil-based bases that are occlusive, emollient, and stays for long time.

Emulsion or water miscible bases: Water-in-oil or oil-in-water emulsions.

Absorbent bases: These include water-in-oil emulsions with aqueous solutions and water-in-oil emulsions with oil-soluble active ingredients.

Water soluble bases: A non-greasy dosage that can be washed down with water; many have a polyethylene glycol base.

1.3.2. Gels

Gels are semi-solid dosage forms that can be applied either by topically or transdermally. They are aqueous colloidal suspensions with a liquid phase that is entangled in a polymeric matrix. Gels tend to be clear or translucent, and their smooth nature makes them easy to apply evenly over the skin surfaces. In addition to being used as a drug, they can also be used as lubrication. Transparent semisolid dosage forms for external use containing hydrophilic or hydrophobic base with gelatinizing agents.

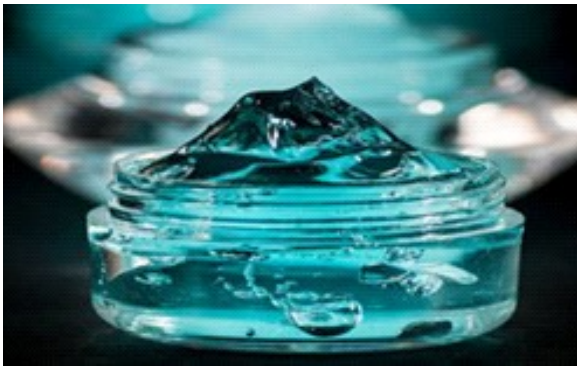

Figure 3: Gel

1.3.3. Creams and Lotions

Creams are also designed for topical use. They're analogues to ointments, but typically have an opaque appearance and more water content and less oil. This makes them less slithery than ointments and easier to spread over large areas of skin. Creams can be water-in-oil or oil-in-water. Creams consists with more than 20% water or volatile factors and typically lower than 50% hydrocarbons, waxes, or polyols as vehicles (Osborne, 2008). Creams are preferred over ointment due to their ease of spreading and removal. They used as a vehicle for drug substance such as local anaesthetic, anti inflammatories, anti-fungal, etc. (Nwoko, 2014). Also correspond of a lipophilic phase and an aqueous phase. Based on continuous phase, there are lipophilic (w/o) and hydrophilic (o/w) creams. Creams are with or without medicaments with suitable adipose base.

Lotions are topically applied preparations, which are appeal to the skin with bare hands or cotton wool, with the intent to moisturise and/or treat the skin. Most body lotions keep the skin soft, smooth and healthy but some of them also helps in anti-ageing and some contains fragrances. Lotions are analogues to creams, but have more water content, making them the lightest of the semi-solid topical dosage forms. Some lotions also contain alcohol.

Figure 4: Cream

1.3.4. Paste

Pastes have a thicker consistency than ointments, as they are admixture of powder and ointment. They are designed for both topical and transdermal applications. They can be delicate to apply evenly and to large areas; as such, pastes are most frequently used to treat localized conditions, like athlete's foot. The major difference between a paste and an ointment is that the former are stiffer and low slithery. They are generally prepared by dissolving the active medicament in different base.

Figure 5: Paste

1.3.5. Poultices

A poultice is a soft, wettish mass that is spread on a cloth and than applied on the skin to treat various problems (such as insect bites, arthritis , boils , infections and more….). It is also called as cataplasms. It

Figure 6: Poultice

should not contain soluble salts. The ready to use mixture should have a pH value of 6-10 maximum at 25° temperature. The mixture should be easy to apply, adhere well, free from dyes or colouring agents. After treatment it should be possible to remove the cataplasm without any residues.

1.3.6. Suppositories

Suppositories are semi-solid dosage forms which are intended through different routes like the rectum, vagina, or urethra. These are not meant for oral use. Vaginal suppositories, also known as pessaries, come in different shapes and sizes. These fit in the vagina and help the vaginal tissues. Urethra suppositories are called Bougies. These are thin, long, cylindrical pencils in shape and are very rarely used. It's substantially used by men facing erection problems. Women's urethral suppositories are comparatively smaller than men's. Among these, rectal suppositories are the most common type of suppository as they can deliver numerous types of medicines.

Figure 7: Suppositories

2. Excipients

An excipient is a substance formulated alongside the active component of a medication, included for the purpose of long-term stabilization, bulking up solid formulations that contain potent active ingredients in small quantities (thus often referred to as "bulking agents", "fillers", or "diluents"), or to confer a remedial improvement on the active ingredient in the final dosage form, such as easing drug absorption, reducing viscosity, or enhancing solubility.

Excipients are substances other than the API which have been appropriately estimated for safety and are intentionally included in a drug delivery system and/or pharmaceutical expression (Ansel *et al.*, 2013). Excipients are the complements used to convert pharmacologically active compounds into pharmaceutical dosage forms suitable for the administration. The International Pharmaceutical Excipients Council (IPEC) defines excipient as "Substances, other than the API in finished dosage form, which have been appropriately evaluated for safety and are included in a medicine delivery system to either aid the processing or to aid manufacture, cover, support, enhance stability, bioavailability or patient adequacy, help in product identification, or enhance any other attributes of the overall safety and effectiveness of the drug delivery system during storage or use."(Chan and Chew, 2007).

> *"The word excipient is derived from the Latin excipere, meaning 'to except', which is simply explained as 'other than'. Pharmaceutical excipients are principally everything other than the active pharmaceutical component. Ideally, excipients should be inert, however, recent reports of adverse reactions have suggested otherwise."* (Rowe *et al.*, 2009).

Excipients are substances that are added to a drug expression to aid in the manufacturing process, improve the stability, or enhance the performance of the drug. In semi-solid dosage forms, excipients such as petrolatum, mineral oil, lanolin, beeswax, and paraffin are generally used as bases or vehicles for the active pharmaceutical component. These excipients help to give a consistent texture and facilitate the absorption of the drug into the skin. we have some pharmaceutical excipients with plant origin like starch, agar, alginates, carrageenan, guar gum, xanthan gum, gelatine, pectin, acacia, tragacanth, and cellulose (Wade and Weller, 1994).

2.1. Ideal Excipient Properties

Excipients range from inert and simple to active and combined substances that can be difficult to differentiate. Traditionally, excipients were mostly structurally simple, biologically inert and stable, and of natural origin such as corn, wheat, sugar, and minerals. Numerous further new and increasingly complex excipients have been developed as new drug formulation delivery systems emerge and evolve. The stable and inoffensive nature of excipients is not preferable in drug formulations. Many excipients are impart toxicants at higher doses in animals, though it's safe in humans at therapeutic doses, including commonly used excipients such as cyclodextrins, dextran, and polyethylene glycol.

Excipients aren't fully inert. Even commonly used excipients that are supposed to be pharmaceutically inactive and nontoxic may cause adverse responses (Smith and Dodd, 1982; Kotkoski *et al.*, 1999).

Apart from the physical and chemical properties it is important the excipients used are pharma grade excipients and comply with the current pharmacopeia's such as Ph. Eur (European Pharmacopeia), USP-NF (United States Pharmacopeia) and JP (Japanese Pharmacopeia). The pharmaceutical grade excipients production also requires the GMP level for excipients.

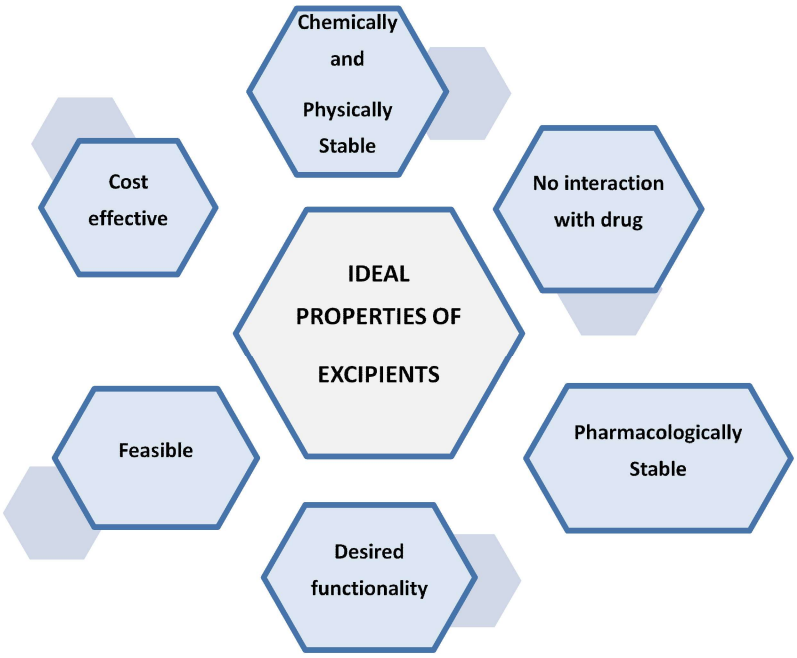

Figure 8: Ideal Properties of Excipients

2.2. Roles of Excipients

Excipients have many roles in a formulation, some of the major ones include:

- Supports in the processing of the drug delivery system during its manufacture.
- Protect, support, or enhance stability, bioavailability, or patient adequacy.
- Help in product identification, and enhance any attribute of the overall safety.
- Oblige in the effectiveness and/or delivery of the drug in use.
- Lift in maintaining the integrity of the drug product during storage.

2.3. What is the Purpose?

- Provide bulk to the formulation.
- Helping in drug absorption or solubility and other pharmacokinetic parameters.

- Aid in handling of API during manufacturing.
- Provide stability and help from denaturation, etc.

2.4. Excipients Used in Semi Solid Dosage Forms

Semi-solid dosage forms, such as ointments, creams, gels, and pastes, are prepared by using different variety of excipients to impart specific properties and characteristics to the formulation. Some common excipients used in semi-solid dosage forms include:

- Surfactants and Emulsifiers
- Thickening agents
- Solvents
- Humectants
- Preservatives
- Antioxidants
- Organoleptic agents
- Gelling agents
- Buffers
- Permeation enhancers
- Bases

2.4.1. Surfactants and Emulsifiers

These help to stabilize and ameliorate the spread capability and uniformity of the product.

2.4.1.1. Surfactants

A surfactant, also called surface-active agent, substance such as a detergent that, when added to a liquid, reduces its surface tension, thereby adding its spreading and wetting down properties. In the dyeing of fabrics, surfactants help the colour access the fabric evenly. Due to their structural peculiarity, surfactants can be extensively used to reduce the surface and interfacial tension between two or more phases.

2.4.1.1.1. Properties of Surfactants

Surfactant when present at low concentrations in a system has the adsorbing property onto the surface or interfaces of the system and of changing to a marked degree, the interfacial free altering to a marked degree, and the interfacial free forces of those interfaces.

2.4.1.1.2. Applications of Surfactants

- The amphiphilic nature of surfactants makes them suitable for use in numerous industrial products, including medicines, corrosion inhibitors for protecting steel and other corrosive metals, detergents, cleansers, de-emulsifiers, wetting agents, oil ...
- Surfactants act as catalysts in numerous metal-mediated oxidation processes (Mondal *et al.*, 2019).
- Surfactants play major role in cleaning, wetting, dispersing, emulsifying, foaming and anti-foaming agents in many practical applications and products, including detergents, fabric softeners, motor oils, emulsions, soaps, paints, adhesives, inks, anti-fogs, skin waxes, snowboard wax, deinking of recycled papers, ...

2.4.1.1.3. Examples Include

Tween 60, Tween 80, Potassium oleate, Polysorbate 80, Glyceryl stearate, Lecithin, Alkyl ether phosphates, Sodium stearate, Benzalkonium chloride, Docusate is another name for dioctyl sodium sulfosuccinate.

2.4.1.2. Emulsifier

Emulsifier, with any of various chemical components that support the suspension of one liquid in another, as in the mixture of oil and water.

2.4.1.2.1. Functions of Emulsifiers

A emulsifier, also called an emulgent, is a surface-active agent that acts as a border between two immiscible liquids similar as oil and water, allowing them to be blended into stable emulsions. Emulsifiers also reduce stickiness, control crystallization and avoid separation.

Anionic Emulsifying Agents

- They carry a negative charge. For example, potassium, sodium, and ammonium salt of lauric and oleic acid are soluble in aqueous solution and are good O/W emulsifying agents.
- Anionic emulsifying wax functions as an emulsifying agent in topical therapeutical products. The typical usage levels are 5-15% (Chang *et al.*, 2013; Karl *et al.*, 2016). It is recommended that the wax is added to lipid or paraffin phases of the emulsion to enable bases to grease smooth addition and manufacture of stable emulsions.

2.4.1.2.2. Disadvantages of Emulsifying Agents

- It needs to be shaken well before use.
- A particular measuring device is needed for administration.
- A degree of specialized delicacy is needed to measure a dose.
- Storage conditions may affect stability.
- Denser, difficult to transport, and leads to container breakages.

2.4.1.2.3. Advantages of Emulsifying Agents

Emulsifying bases retain special properties not shared by other ointment bases, such as their miscibility with fluid, their texture, impartiality, stability, and capacity to combine the physically contra indicatory.

2.4.1.2.4. Uses of Emulsifying Agent

Emulsifiers will form and stable oil-in-water emulsions (e.g., mayonnaise), uniformly disperse oil-soluble flavour compounds throughout a product, prevent large ice-crystal formation in frozen products (e.g., ice cream), and improve the volume, uniformity, and fineness of baked products.

2.4.1.2.5. Classification of Emulsifying Agents

1. Emulsifiers made from natural ingredients:

   Animal sources: Wool fat, Gelatine, etc.

   Vegetable sources: Agar, Tragacanth, Gum acacia, etc.
2. Emulsifying agents that are semi-synthetic:

   For example, methylcellulose and sodium carboxymethyl cellulose.
3. Emulsifying agents derived from synthetic materials are:

   Inorganic emulsifying agents: Milk of magnesia.

   Cationic emulsifying agents: Benzalkonium Chloride.

   Anionic emulsifying agents: Sodium lauryl sulfate (SLS).

   Non-ionic emulsifying agents: Glyceryl ester.

2.4.1.2.6. Examples Include

Soy lecithin, Carrageenan, Mono- and diglycerides, Carboxymethylcellulose, Polysorbate, Sodium lauryl sulphate, Triethanolamine, Wool fat, Gelatin, Benzalkonium chloride.

Figure 9: Emulsifying Agents

2.4.2. Thickening Agents

These help to increase the viscosity and impart a smooth and compatible texture to the product.

2.4.2.1. Advantages of Thickening Agents

A thickening agent or thickener is a substance which can enhance the viscosity of a liquid without any particular changes its other properties. Edible thickeners are generally used for thickening sauces, soups, and puddings without altering their taste; thickeners are also used in paints, inks, explosives, and cosmetics.

2.4.2.2. Disadvantages of Thickening Agents

Thickened liquids also cause individuals to feel full faster thus often not consuming as important other food as they need. Thickeners can change the taste of the liquid causing individuals to refuse to drink it. Thickeners can also be very constipating.

2.4.2.3. Characteristics of Thickening Agent

Thickening agents, or thickeners, are hydrocolloids that increase the viscosity of a solution or mixture without significantly affecting its other properties, similar as taste. Hydrocolloids are a heterogeneous group of long-chain polymers that, when dispersed in water, produce a thickening or viscous and gelatinizing effect.

2.4.2.4. Uses of Thickening Agents

Thickening Agent in Suspension is a liquid that helps keep other substances in suspension. Its main function is to prevent the solids to sediments at the bottom of the container. A good example of an organic liquid suspended in water is poly (ethylene glycol).

2.4.2.5. Examples Include

Carbomers, hydroxyethyl cellulose, xanthan gum, Corn Starch, Pectin, Potato Starch, Tapioca Starch, Arrowroot, Acacia gum.

2.4.3. Solvents

- These are used to dissolve or disperse the active component and other excipients.
- A solvent is a substance that dissolves a solute, results in a solution. A solvent is usually a liquid but sometimes it can also be present in solid, a gas, or a supercritical fluid forms.
- There are two types of solvents:
  - Organic solvents and
  - Inorganic solvents.

Figure 10: Examplesof Thickening Agents (Corn Starch, Xanthum Gum, Arrowroot)

2.4.3.1. Characteristics of Solvent

- Solvent has the low boiling point and gets efficiently dissoluted.
- Solvent have shadings and smells.
- Most of the solvents are liquids, but few of them can stay in a gaseous state.
- Solvents help to manage the temperature of a solution.
- Solvents are changeable in nature.
- The solvent should be volatile, affordable, and non-inflammable.
- The solvent should possess the dissolving the impurities or not at all.
- If the solvent dissolves the impurities present in a solid sample, then the impurities will not be present in the crystal structure of the solid.
- Water is called the "universal solvent" because it is capable of dissolving further substances than any other liquid. This is necessary to every living thing on earth. It means that wherever water goes, either through the air, the ground, or through bodies, it takes along some of the expensive chemicals, minerals, and nutrients.

2.4.3.2. Applications of Solvents

Some of the most common uses of organic solvents include chemical synthesis, apparel dry cleaning, paint thinners, nail polish and glue removers as well as cleansers.

Figure 11: Examples of Solvents (Ethanol, Propylene Glycol)

2.4.3.3. Examples Include

Propylene glycol, Water, Methanol, Acetone, Toluene, Methyl acetate, Ethyl acetate, Ethanol, Polyethylene glycol.

2.4.4. Humectants

These help to retain moisture and help the product from drying out. The humectant is a hygroscopic substance used to increase the solubility of the active component to increase skin penetration. It's also used to increase the hydration of the skin.

2.4.4.1. The Risk of Using Humectants on Your Skin

A few examples of these problems are accelerated aging, skin flaking, and uncontrolled drying.

2.4.4.2. Benefits of Humectants

- Helps maintain moisture content in skin, preserves overall properties of products, helps to seal cracks in skin, exfoliates, and removes dead skin cells. In general, humectants can help all skin types.
- The benefits of humectants depend on the component. In general, the side effects may include relief of dry skin, reduction of thickened skin, and strengthening of the skin barriers.
- Humectants are different from emollients and occlusives. These ingredients are also used in many personal care products for curing the dry skin problems.

2.4.4.3. Characteristics of Humectants

- A humectant is a common moisturizing agent present in lotions, shampoos, and other beauty products used for your hair and skin. They're known for their capability to retain moisture while also storing the overall properties of the product at hand.
- Humectants are necessary to effectively moisturize the skin, they're especially needed for those with dry skin. But humectants can be helpful for any skin type, since all need some degree of hydration (even oily skin).
- All humectants bind with water, but some of them have an additional role or bind with other solvents. Some humectants first break down the dead skin cells congesting up your skin's surface. Once the humectants loosen the dead cells of dry skin, they draw moisture from deeper layers of skin.

2.4.4.4. Examples Include

Glycerine, Sorbitol, Propylene glycol, Hyaluronic acid, Urea, Stearic acid, Triethanolamine, Polyethylene glycol, Lactic acid, Propylene glycol, Aloe vera.

Figure 12: Some Examples of Humectants (Aloevera, Sorbitol, Glycerin)

2.4.5. Preservatives

A preservative is a substance that is added to final products such as personal hygiene products, foods and beverages, pharmaceuticals, wood, biological material, etc., to avoid decomposition by microbial growth or by undesirable chemical changes.

2.4.5.1. Classification of Preservatives

Table 2: Classification of Preservatives (Kumar *et al.*, 2023)

Preservatives				
Based on Mechanism of Action			Based on Source	
Antioxidants	Antimicrobial Agents	Chelating Agents	Natural	Artificial
The agent which prevent oxidation of active pharmaceutical ingredient which undergoes degradation due to oxidation as they are sensitive to oxygen.	The agent which active against gram positive and gram negative micro organism which causes degradation of pharmaceutical preparation.	The agents which form the complex with pharmaceutical ingredient and prevent the degradation of pharmaceutical formulation.	These drugs are obtained by natural sources like plants, animals and mineral sources etc.	These preservatives are man made by chemical synthesis active against by various micro organisms in small concentration.
Examples: Vitamin E, Vitamin C, Butylated hydroxy anisole (BHA), Butylated hydroxy toluene (BHT)	Examples: Benzoic acid, Sodium benzoate, Sodium paraben, Ethyl paraben, Propyl paraben, Alcohols, Phenols	Examples: Ethylene diamine tetra acetic acid (EDTA), Polyphosphates, Citric acid	Examples: Neem oil, Sodium chloride salt, Lemon, Honey	Examples: Benzoates, Sorbates, Propionates, Nitrites

2.4.5.2. Uses of Preservatives

- The use of preservatives in medicines such as acetaminophen, insulin, and cough syrup will helps in prevention of microbial contamination.
- The purpose of adding preservatives to the preparations is to prevent the growth of microorganisms, such as bacteria and fungi, that may generate disease or infection.
- These are added to enhance the shelf life of the product.
- Preservatives are added substantially to prevent the growth of organisms and to keep the drug stable by preserving from microorganisms for a longer period of time.

2.4.5.3. Side Effects of Preservatives

- Induced breathing problems like asthma;
- Hyperactive behaviour in children;
- Weakened heart tissue;
- Contain cancer-causing food complements such as BHA and BHT;
- Increase the chances of obesity;
- Loss of important nutritive value;
- Headaches;
- Alterations in mental concentration;
- Cancer;
- Cardiovascular disease;
- Other degenerative conditions.

There is a possibility that the excess use of artificial preservatives could leads to some of the signs and symptoms of GERD, including:

- Heartburn;
- Difficulty swallowing;
- Regurgitation;
- Gas and bloating;
- Pain or discomfort in the chest;
- Intolerance of certain foods and liquids.

2.4.5.4. Benefits of Preservatives

The main application of natural preservatives in the industry is to resist the growth of undesirable microorganisms. It is possible to add plant antimicrobials into the product formulation, coat them on the surface of preparations, or incorporate them into the packaging material.

2.4.5.5. Examples Include

- Anti microbial preservatives: Phenols, Benzoic acid, Sorbic acid, Methylparaben, Propylparaben, quaternary ammonium salts and other compounds.
- Generally used preservatives: Benzalkonium chloride, methyl hydroxy benzoate, propyl hydroxy benzoate, chlorocresol, phenyl mercuric nitrate, potassium sorbate.

2.4.6. Antioxidants

- These are used to reduce oxidation and degradation of the active ingredient and other excipients.
- The most common antioxidant complements are ascorbic acid and ascorbates (Bhat Rajeev *et al.*, 2011). Thus, antioxidants are commonly added to oils, cheese, and chips. Other antioxidants include the phenol derivatives BHA, BHT, TBHQ and Propyl gallate. These agents suppress the formation of hydroperoxides (Dalton Louisa, 2002).
- Oxygenis one of the major reactive atoms, that has the ability to interact and become part of potentially damaged molecules called "Free radicals." These free radicals can attack the healthy cells of the body and can change their structure, which leads to their disfunctions.
- They are self reducing agents that oxidize themselves and reduce oxidation of the components that are sensitive to oxygen.

These are three main types:

Table 3: Types of Antioxidants (Rowe *et al.*, 2009)

True Antioxidants (Water Insoluble)	Reducing Agents (Water Soluble)	Antioxidant Synergists (Chelating Agents)
They act by a chain-termination mechanism by reacting with free radicals. E.g.: Butylated hydroxy anisole (BHA), Butylated hydroxy toluene (BHT)	They have a lower redox potential than the drug and get preferentially oxidized. E.g.: ascorbic acid. Thus, they can be consumed during the shelf life of the product.	These enhance the effect of antioxidants. E.g.: EDTA (ethylene diamine tetra acetic acid). Tetra acetic acid derivatives and salts, dihydroxyethyl glycine, citric acid, and tartaric acid.

2.4.6.1. Role of Antioxidants

- Antioxidants are used as medicinal excipients to help conflict the deterioration of drugs. Antioxidants are extreme class of preservatives. Some of the preservatives with antioxidant effects include: L-(+)-Ascorbic Acid, Ascorbyl Palmitate, Butylated Hydroxytoluene, etc.

- Antioxidants scavenge free radicals from the body cells and reduce the damage caused by oxidation. The defensive effect of antioxidants continues to be studied around the world.
- Antioxidants are excipients which are used to enhance stability of medicines by delaying the oxidation of active substances and other excipients. Antimicrobial preservatives are typically added to avoid microbial proliferation arising under in use conditions.

2.4.6.2. Uses of Antioxidants

Antioxidants fight with free radicals present in your body. Free radicals are compounds that can produce harm if their levels become too high in your body. They're connected to multiple diseases, including diabetes, heart disease, and cancer. Your body has its own antioxidant defences to keep free radicals safe.

2.4.6.3. Side Effects of High Antioxidants

- High-dose supplements of antioxidants may be leads to health risks in some cases. Supplementing with high doses of beta-carotene may increase the threat of lung cancer in smokers. Supplementing with high doses of vitamin E may promote risks of prostate cancer and other type of stroke.
- Common side effects of over-intake of antioxidants are diarrhoea, dizziness and joint pain. There is also a witness of yellow pigmentation of the skin due to the antioxidant carotene. Another rare side effect is discoloration under the skin. Cooking some foods may increase or decrease their antioxidant levels in the food.
- These responses lead to the production of ROS, RNS and RSS whom have been linked to various diseases like cancer, cardiovascular diseases including atherosclerosis and stroke, neurological disorders, renal disorders, liver disorders, hypertension, rheumatoid arthritis, adult respiratory suffering syndrome, auto-immune diseases.
- Though in normal physiological condition the generation of reactive species are tightly regulated by different enzymatic and non-enzymatic antioxidant, but overproduction of ROS results in oxidative stress, which is important intermediary of damage to cell structures, including lipids and membranes, proteins, and DNA (Valko *et al.*, 2007; Fang *et al.*, 2002).

2.4.6.4. Examples Include

Butylated hydroxyanisole (BHA), Potassium and sodium metabisulfite, Thiosulfate, Butylated hydroxy toluene (BHT), Ascorbic acid.

2.4.7. Organoleptic Agents

Organoleptic agents contribute an important role in the field of pharmaceutical excipients. These agents encompass a range of additives responsible for colouring, flavouring, sweetening, and texturing preparations.

2.4.7.1. Importance of Organoleptic Additives

Organoleptic additives promote appearance and palatability of pharmaceutical dosage forms. If the product does not have acceptable colour, flavour and taste, the patient would try to avoid using it.

2.4.7.2. Organoleptic Properties

The organoleptic properties include drug substance appearance, colour and odour, while the bulk properties include density, cohesivity or flow ability distortion, moisture content and particle packing.

2.4.7.2.1. Flavouring Agents

- These are added to ameliorate the aesthetic appeal of the product and enhance patient acceptance.
- Flavouring agents in pharmaceutical preparations similar as oral syrup, oral suspension, elixirs, emulsions, dosages, chewable tablets, effervescent tablets, dispersible tablets, and ODT are used to conduct not only flavours but also impart a pleasant taste.
- They are used to enhance patient compliance or palatability of pharmaceutical dosage forms.

- Generally, flavouring agents (pharma grade) are available in two forms: a) powder, and b) liquid form.
- The word flavour refers to a mixed sensation of taste, smell, touch, sight, and sound, all of which combine to get an unrestricted number of gradations in the perception of a chemical substance.
- The 4 primary tastes: a) saline, b) sour, c) bitter, and d) sweet appear to affect incompletely from psychological action and partly from physicochemical (Remington Joseph and Paul Beringer, 2005).

2.4.7.2.1.1. Classification of Flavouring Agents

On the basis of sources

A. Natural flavouring agent;

B. Artificial or synthetic flavouring agents;

C. Natural and Artificial flavouring agents;

On the basis of physical form

A. Solid flavouring agents;

B. Liquid flavouring agents;

2.4.7.2.1.2. Advantages of Flavouring Agents

Flavouring agents are cumulative substances that give a tablet an additional taste or flavour. In particular, they help in masking unpleasant tastes (e.g., bitter or pungent taste) of drugs/excipients and rather ameliorate the quality of their taste.

2.4.7.2.1.3. Disadvantages of Flavouring Agents

- May cause hyperactivity in kids.
- May cause allergic reactions.
- Add-on compounds can contribute to high blood pressure.
- Additives can make you obese.

2.4.7.2.1.4. Examples Include

Methionine, Maltol, Ethyl maltol, Denatonium benzoate, Ethyl acetate, Ethyl lactate, Monosodium glutamate, Adipic acid, Dibutyl sebacate.

Figure 13: Flavouring Agents

2.4.7.2.2. Colouring Agents

- Colorants are substances that adds colour to other substances that are devoid of colour (transparent, white, or grey) or modify the colour of a coloured substance. Moreover, some chemicals that have no colour but react with another substance and produce colour are called colour additives.
- For example, dihydroxyacetone (DHA) reacts with the skin protein and imparts colour.

2.4.7.2.2.1. Classification of Colouring Agents

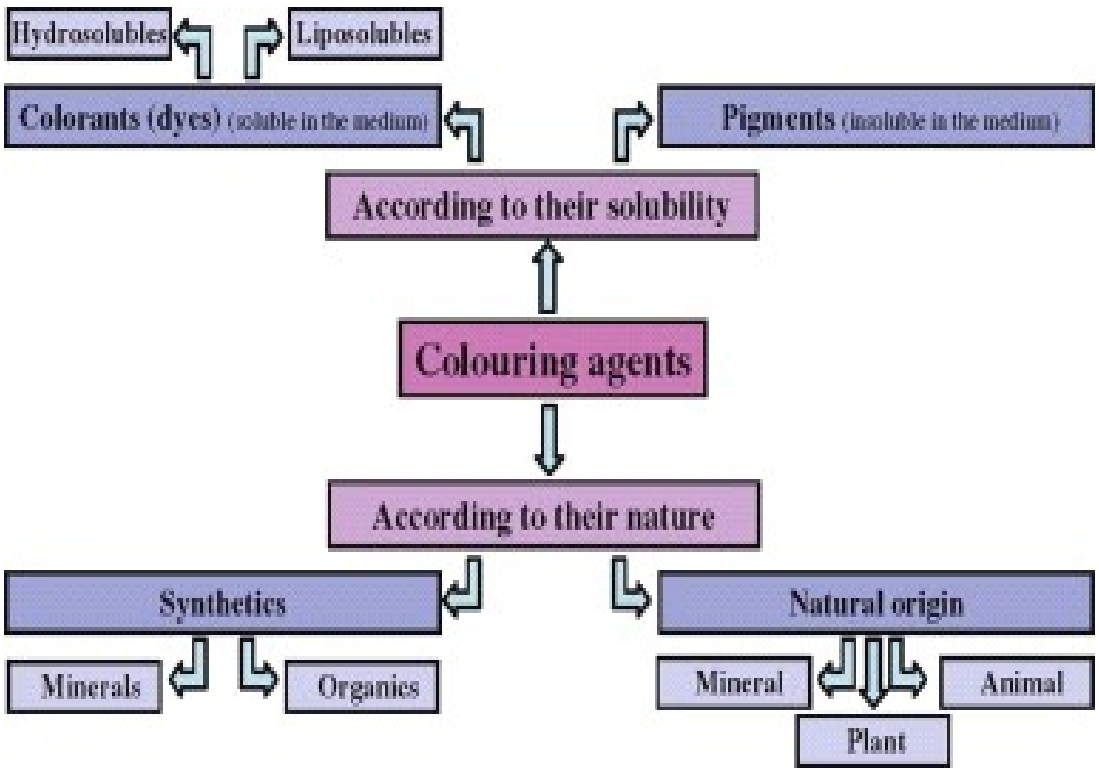

Figure 14: Classification of Colouring Agents

2.4.7.2.2.2. Applications of Colouring Agents

- Colouring agents are added to cosmetics in order to colour the cosmetic itself and/or to impart colour to the skin (or its accessories) of users of decorative cosmetic products.
- Colorants or colouring agents are used in the processing of food, drugs and cosmetics and are regulated by the U.S. Food and Drug Administration to ensure safety.
- A colour additive is any dye, pigment or substance which are added to a food, drug or cosmetic, or to the human body will impart a colour.
- Colouring agents are to avoid counterfeiting. To enhance patient acceptance because unattractive drug products can be made more acceptable to the patient.
- Colouring agents can also be used to make preparation more uniform when an component in the formulation has a variable appearance from batch to batch.
- Coloring agents are incorporated into food products to improve sensory characteristics, compensate for color loss during processing, and influence consumers' perceptions of flavor and quality (Damodaran *et al.*, 2007).

2.4.7.2.2.3. Disadvantages of Colouring Agents

Some artificial colours have been linked to health disturbances such as hyperactivity in children, cancer, and antipathetic reactions.

2.4.7.2.2.4. Examples Include

Table 4: Examples of Colouring Agents

Colouring Agent	Colour	Source
Anthocyanins	Orange-Red to Red to Blue	Berries, Grapes, Apples, Roses, Hibiscus, Red Cabbage, Sweet Potato
Betacyanins	Red	Red Beets, Red Chard, Cactus Fruit, Bougainvillea
Caramel	Beige to Brown	Heated Sugars
Carmine	Red	Cochincal Insects
Carotenoids	Yellow to Orange to Red	Saffron, Tomatoes, Paprika, Corn, Butter, Palm Oil
Chlorophylls	Green to Olive Green	Green Plant Leaves
Riboflavin	Yellow	Vegetables Leaves, Milk ,Eggs, Organ Meats, Malt
Turmeric	Yellow	Curcuma Longa Rhizomes

2.4.8. Gelling Agents

- Gelling agents are polysaccharides, which have the capability to form gels. We can also call them solidifiers as they give a semi-solid structure, helping in maintaining the texture of the formulation.
- In semisolid dosage form, gelling agents are used at a range of 0.5%-10%.
- The gelling agent which forms network by interlinking particles affect in the rigidity of gel (Florence and Attwood, 2011; Cooper and Gunn, 2000).

Table 5: Concentrations of Different Gelling Agents

Gelling Agents	Concentration Used (%w/w)	Pharmaceutical Adaptability	Active Pharmaceutical Ingredient
Sodium CMC (Perioli *et al.*, 2009)	3-4%	Stand autoclaving hence suitable for sterile gels	Benzydamine
Carbopol-934 (Deveda *et al.*, 2010)	1%	Provide controlled release of API incorporated	Chlorphenesin
Carbopol-940 (Khullar *et al.*, 2011)	1%	Because of high viscous gel, provide controlled release of API incorpated	Mefenamic acid
HPMC (Mohamed, 2004)	2.5%	Having good stability, microbial resistance	Clorphenesin
Combination of HPMC & Carbopol (El-Setouhy and El-Ashmony, 2010; Shahin *et al.*, 2011)	1.2%	Combination improve stability	Ketorolac, clotrimazole
Pluronic F127 (Shokri *et al.*, 2012)	1-3%	Good clarity and better solubility in cold water	Piroxicam
Pemulen (Perioli *et al.*, 2008)	0.1-0.4%	Provide rapid release of oil phase, excellent stability	Flubiprofen

2.4.8.1. Advantages of Gelling Agents

- Gelling agents also serve as stabilizers and thickeners to give thickening without stiffness through the formation of gel in jellies, jams, desserts, yogurts and candies.
- Generally, gelling agents are used to increase the consistency of formulation and improve sensitive properties

by making these systems thixotropic. The gelling agents also show effect on the release of active substances from the formulation and stability of the system.

2.4.8.2. Disadvantages of Gelling Agents

There is one limitation to the use of gelling agents. Large amounts of the material must often be applied, as much as three times the volume of the spill. For oil spills of millions of gallons it is impracticable to store, move, and apply such large amounts of material.

2.4.8.3. Importance of Gelling Agent

Gelling agents are important in cell and tissue culture because they give a structured support for growth. Gelatin was the first gelling agent discovered, and it paved the way for agar, phytagel, and other gelling agents with properties well suited for biotechnology.

2.4.8.4. Examples Includes

Tragacanth, Starch, Carbomer, Gelatine, Cellulose derivatives, Pectin, Polyvinyl alcohol clays, Sodium alginate, etc.

2.4.9. Buffers

- Creams and ointments, when kept under storage for a long time, may encounter pH changes and can reduce the stability of formulations.
- Buffers such as citric acid, sodium citrate, or phosphoric acid or sodium phosphate, are added during the process for maintaining stability.
- Buffers are added for various purposes. Such as:
  i. Compatibility with skin
  ii. Drug solubility
  iii. Drug stability
  iv. Influence the ionization of drugs

2.4.9.1. Advantages of Buffer Solution

- The major advantage of a buffer is that it is keeps the pH stable and improve the solubility of the formulation.
- Buffer solution plays a significant part in chromatography, as retention of ionizable molecules is extremely sensitive to the pH of the mobile phase in similar cases the pH can be regulated by adding a buffer solution.
- The buffer solution can remain stable for several weeks if it is stored in the cool frozen containers.
- Some of the buffers such as acetate, ammonium, sodium, and phosphate, etc., are highly soluble in universal solvent.
- The pKa (ionisation factor) of a buffer solution is maintained same as being body fluids; hence it is used in the dissolution testing to determine the extent and rate of solution formation from a dosage form (Brown *et al.*, 2008).
- It maintains the solubility of the remedial agent in the pharmaceutical product.
- Buffer solution enhances the stability of products where the active component is pH-dependent.
- It is non-toxic to cells and inhibits enzymatic reactions.
- The onset of action of dosage form increases by using the buffer solution.
- A buffer is a solution that can endure pH change upon the addition of an acidic or basic components. It is able to neutralize small quantities of more acid or base, thus maintaining the pH of the solution relatively stable. This is important for processes and/or reactions which holds specific and stable pH ranges.
- It is used to optimize biological activity.

- Since the pH of the buffer solution is accurate, standard buffers i.e. pH 07.00, 04.00, and 09.20 are used to calibrate the analytical instruments (pH meter).

2.4.9.2. Disadvantages of Buffer Solution

- However, they have a number of implicit disadvantages: Phosphates inhibit numerous enzymatic reactions and procedures that are the foundation of molecular cloning, including breakdown of DNA by many restriction enzymes, ligation of DNA, and bacterial transformation.
- The major disadvantage of the buffer solution is that it is an aqueous solution the contamination is more and is not suitable for long-term storage, so preparation of a fresh buffer solution is needed each time.
- To acclimate the pH of the solution, it is necessary to know the pKa value of the element.
- The drug dissolution may precipitate when the pH of the solution is not maintained correctly.
- Some types of the buffer are retained and tend to react.
- Medicinal constituents and some vitamins are dissolved only at a particular pH therefore, it is essential to maintain the correct pH of the solution.

2.4.9.3. Applications of Buffers in Pharmacy

- Not only do they perform to regulate shifts in pH, they also can stabilize proteins by a variety of mechanisms. The ability of buffers to stabilize remedial proteins whether in liquid formulations, frozen solutions, or the solid state is highlighted in this review.
- In the pharmaceutical field, natural buffers are usually used to maintain the specific pH value. Ensure the stability of drug components: Maintain the pH value of essential factors of the drug from being changed or degraded by the gastrointestinal environment, similar as aspirin.
- Phosphorus keep the bones strong and healthy. And also helps to remove waste and repair damaged tissues. Most people get enough phosphorus through their diet. However, people with certain health conditions, such as kidney disease or diabetes, may need to add-on phosphorus intake in their diet.
- Phosphate is the salt form of phosphorus. Some phosphates are used to make the urine more acidic, which helps to treat certain urinary tract infections. Some phosphates are used to prevent the formation of calcium stones in the urinary tract.
- Buffer solutions are utilized in the pharmaceutical industry to ensure impeccable purity, heightened stability, improved solubility, and optimal biological activity of compounds and products.

2.4.9.4. Examples Include

Sodium acetate, sodium citrate, potassium meta phosphate, etc.

2.4.10. Permeation Enhancers

- These compounds increase transdermal drug delivery by disquieting the stratum corneum (SC) and/or other components of the skin.
- Skin penetration enhancers may develop SC diffusion coefficient of the drug or promotes the vehicle drug effective concentration.
- They can also interact with keratin to increase transport through the corneocytes or ameliorate the partitioning of drug in the SC.

2.4.10.1. Advantages of Permeation Enhancers

- Dendrimers have the advantage of skin permeation improvement.
- Advantages of the transdermal delivery methods include the capability to administer compounds continuously over relatively long periods of time without repeated invasive procedures.

2.4.10.2. Disadvantages

Include difficulty with administering and maintaining appropriate doses of drugs.

2.4.10.3. Applications

The application of permeation enhancers (PEs) to improve transport of inadequately absorbed active pharmaceutical ingredients across the intestinal epithelium is aextensively tested approach.

2.4.10.4. Principle of Permeation Enhancers

- The applicable Vitamin C content in cosmetic formulations is greater than 8% for it to be biologically significant (Kim *et al.*, 2017) .
- Commonly, VC topical products on the market today have an ascorbic acid content that varies from 10 to 20% (Telang, 2013).
- The most known mechanism of skin permeation enhancement of dendrimers is their commerce with skin lipids and denaturation of keratin proteins which could get better trans-cellular saturation of active pharmaceuticals.
- Chemical enhancers help in permeation across the skin by interference of the highly ordered structure of stratum corneum lipid, interaction with intercellular protein or improve partition of the drug into stratum corneum.
- Chemical permeation enhancers (CPEs) are molecules that interact with the ingredients of skin's outermost and rate limiting layer stratum corneum (SC), and increase its permeability. Designing and testing of new CPEs is a resource concentrated task, thus limiting the rate of discovery of new CPEs.
- The selection of chemical permeation enhancers (CPEs) should facilitate the enhancement of drug penetration and deposition while protecting the drug from photo degradation. CPEs alter the skin barrier by partitioning into the stratum corneum (SC) and interacting with its components to temporarily reduce its occlusive properties and facilitate topical drug transport (Kovácik *et al.*, 2020).

2.4.10.5. Examples of Some Permeation Wnhancers Used are

Saponins, Laureth-9, Fusidic acid derivatives, Trihydroxy salts (bile salts), Oleic acid, Caprylate, Laurate, EDTA, Salicylic acid, Phospholipids, etc.

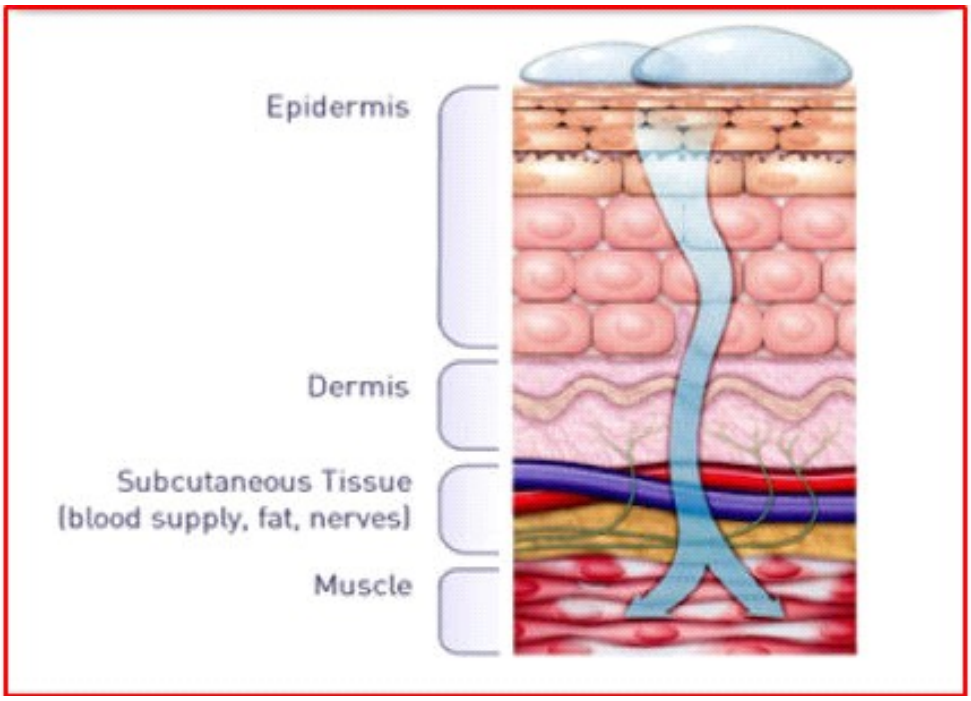

Figure 15: Mechanism of Permeation

2.4.11. Bases

- A base is a substance that can neutralize the acid by interacting with hydrogen ions. Most bases are minerals that react with acids to form water and salts. Bases include the oxides, hydroxides and carbonates of metals.
- It is one of the most important excipients used in the formulation of the semisolid dosage form. Ointment bases do not simply act as the carriers of the medicaments, but they also control the extent of absorption of medicaments incorporated in them.

2.4.11.1. Ideal Characterization of Bases Used in Semisolid Dosage Form

They should be:

- Inert, non-irritating, and non-sensitizing.
- Agreeable with skin pH and the drug.
- Good solvent and/or emulsifying agent.
- Emollient, defensive, non-greasy and simply removable.
- Release medicament readily at the point of application.
- Pharmaceutically elegant and retains good stability.

2.4.11.2. Classification of Bases

According to USP, bases are classified into four general groups:

- Emulsifying bases (oil in water)
- Water Hydrocarbon bases (oleaginous bases) (Petrolatum, Paraffin, Lanolin, etc.)
- Absorption bases (cold cream, anhydrous lanolin, etc.)
- Water-removable-soluble bases (polyethylene glycol).

Classification of Bases

Hydrocarbon or oleaginous bases: The consists of combination of more than one oleaginous material such as a water insoluble hydrophobic oils and fats. This bases are dehydrated and hydrophobic in nature. They are anhydrous, do not absorb water, readily insoluble in water, non-washable. They are highly compatible, occlusive, good emollient. Their application is avoided on infected skin. They can remain on skin for more time period without drying.Oil-based bases that are occlusive, emollient, and stays for long time. (E.g., Hard paraffin, Liquid paraffin, White ointment, White petrolatum).

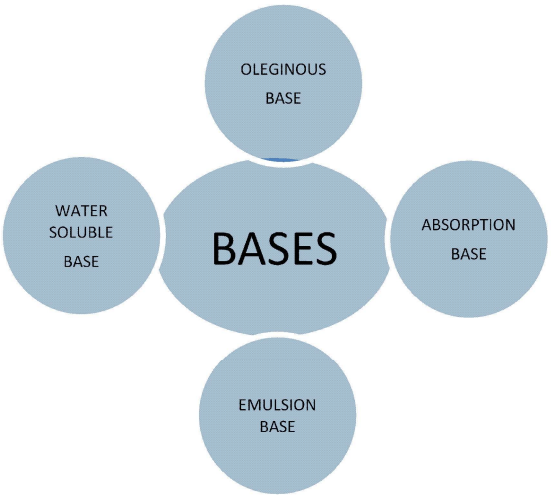

Figure 16: Classification of Bases

Emulsion or water miscible bases: Emulsifying Bases are oil-in-water and water-in-oil bases.

- Oil in water bases: The introductory properties of these bases include their hydrous, water soluble, water absorbable, water washable in nature. Example of this bases acting as drug carrier or vehicle includes PEG ointment, Poly bases, etc.
- Water in oil emulsion bases: These bases are hydrous, hydrophilic in nature, absorb Water, and cannot washed. Their thermal conductivity and occlusive property is less. Some of their properties are analogues to that absorption bases. (E.g., cold cream type, hydrous lanolin, rose water ointment, and hydro cream).

Absorption bases: These are anhydrous bases which maintain their ointment like consistency indeed after absorbing a huge quantum of water. They have capacity to absorb considerable amounts of water or aqueous solution and to water in oil without particular changes in consistency. Their application include their use as emollients and vehicle for aqueous solution and solid drugs. These include water-in-oil emulsions with aqueous solutions and water-in-oil emulsions with oil-soluble active ingredients. These bases are further divided into two types.

i. Non-emulsified bases: These bases produces w/o emulsion by absorbing water and aqueous solutions. (E.g., Wool fat, Wool Alcohol, Beeswax, and cholesterol).

ii. Water in oil emulsion bases: These bases are same as non-emulsified bases with respect to their properties. However they absorb comparatively large quantum of water. (E.g., hydrous wool fat).

Water soluble bases: As the name "Grease less" means oil free. They show complete solubility in water. They are hydrated as well as dehydrated in nature. A non-greasy dosage that can be washed down with water; some have a polyethylene glycol base. (E.g., PEG, Polysorbates and Macrogols (mixture of water and condensation products of ethylene oxide)).

2.4.11.3. Various Types of Bases

Table 6: Various Types of Bases (Allen Jr. and Popovich, 2014)

Types of Bases	Characteristics	Examples	Applications
Hydrocarbons or Oleaginous Bases	Anhydrous Water Soluble Form Occlusive Film on Skin Non-Water Washable Long Lasting	Petroleum Wax Synthetic Esters Like Glycerol Monosterate.	Incorporation of Hydrophobic Drugs
Absorption or Adsorbent Bases	W/O Emulsion or Oleaginous Bases that allow Incorporation of Aqueous Solution to Form W/O Emulsion. Not Easily Water Washable.	Anhydrous: Hydrophilic Petrolatum and Lanolin W/O Emulsion: Lanolin and Cold Cream	Emollients
Emulsion or Water Miscible Bases	O/W Emulsion Leave a Hydrophobic Film on the Surface of the Skin when Water Evaporates	Hydrophillic Ointment Vanishing Cream	Drug Carriers Foundation for Makeup
Water Soluble Bases	Hydrophillic Polymer E.g.: (Peg) Mixture	Peg 400 + Peg 4000 in 40:60 Ratio Propylene Glycol + Ethanol with 2% W/W Hpc	Drug Carriers

2.4.11.4. Importance of Bases

In compounding, the base is the actual cream or gel we put. It's the vehicle that holds the active constituents together and the driver that gets them where they need to be in your body.

2.4.11.5. Advantages and Disadvantages of Bases

Advantages

- The advantage of allowing the blending of drugs with poor water solubility, reducing nasolacrimal drainage and minimization of tear dilution. White and liquid petrolatum's are commonly used as bases for ophthalmic formulations.

Disadvantages

- They are bulkier than solid dosage forms. When applications of an exact volume of ointment to the affected area is needed, it is difficult to ascertain the same.
- These are less stable than solid dosage forms.

2.4.11.6. Advantages and Disadvantages of Absorption Bases

Absorption bases are more hydrophilic than oleaginous base.

Advantages

- High water absorption;
- More spreading;
- Good emollient effect;

Disadvantages

- Hard to remove;
- Cannot apply to exudates area;
- Examples: Anhydrous absorption bases.

2.4.11.7. Advantages and Disadvantages of Hydrocarbon Ointment Bases

Advantages

- They are not absorbed by the skin. They remain on the surface as barrier that restricts the loss of moisture from skin results in softer skin.
- They are sticky in nature thus ensures prolonged contact between skin and medicament.
- They are mostly inert.
- They can resist heat sterilization; hence, sterile ophthalmic ointments can be prepared with it.
- They are readily available and cheap.

Disadvantages

- It may lead to water logging followed by saturation of the skin if applied for a prolonged period.
- It retains body heat, which may produce an uncomfortable feeling.

Suppository Bases

- There is a special base type which is intended internally.
- Suppository bases relate to substances that can be used in preparation of suppositories. Suppository refers to a solid medication with active component made of medicine and a suitable matrix with a certain shape for intracavitary administration. These are solid at room temperature. After being inserted into the cavity, they can quickly soften and melt or dissolve in the secretion fluid by body temperature, and gradually

release the drug to produce local or systemic effects. In the early days, people believed that suppositories only had local effects such as lubrication, antibacterial, insecticidal, astringency and local anaesthesia. Later, it was discovered that suppositories could still absorb drugs through the rectum to exert systemic effects and avoid the first pass effect of the liver.

Types of Suppository Bases

- The commonly used bases for suppositories are divided into-grease bases and water-soluble bases.

Grease Bases

(1) Cocoa butter: Cocoa butter is homogeneous and mixed. It has three crystal forms -α, β, and γ. Among which, α and γ crystal forms are unstable, the melting point is low, and the ? type is stable.

(2) Semi-synthetic or fully-synthetic fatty acid glycerides: Commonly used are semi-synthetic coconut oil esters, lime oil esters, and palm oil esters. completely synthetic fatty acid glycerides include propylene glycol stearate etc.

Water-Soluble and Hydrophilic Bases

(1) Glycerin gelatin: This strain is combination of gelatine, glycerine and water. It is elastic or not easy to break, and does not melt at physiological temperature, but it can be slowly dissolved in the secretion. The dissolution rate of the drug can be changed with water, gelatin and glycerin. The ratio of the three is different. For easy dissolution, the content of glycerine and water should be high.

(2) Polyethylene glycols: It's a type of hetero-chain polymer formed by the polymerization of ethylene oxide. Easy to be damaged by moisture absorption.

(3) Non-ionic surfactants: Based on hydrophilic groups, these are classified as two types: polyoxyethylene type and polyol type. Polyoxyethylene type, also known as polyethylene glycol type, is the product of the addition response of ethylene oxide and composites containing active hydrogen; polyol type non-ionic surfactants are sorbitol, ethylene glycol, pentaerythritol, glycerol and an ester formed from an organic substance containing multiple hydroxyl groups such as sucrose and a higher fatty acid. The hydrophilic group is a hydroxyl group in the molecule. Since the hydroxyl group is weakly hydrophilic, it is frequently used as an emulsifier.

2.4.11.8. Uses

Bases impart the required consistency to topical or transdermal formulations such as creams and ointments and provide effective penetration and absorption of the active pharmaceutical components into the layers of stratum corneum or deeper layers of skin.

Table 7: Common Excipients Used in Various Semi Solid Dosage Forms (Gupta and Garg, 2002)

Ointments	Paste	Cream	Gel
Ointment Base	Paste Base	Penetration Enhancer	Gelling Agents
Preservatives	Preservatives	Oil/Oleaginous Substances	Preservatives
Anti-Oxidant	Anti-Oxidant	Emulgents	Hygroscopic Substances
Chelating Agent	Perfume	Co-Emulsifiers	Chelating Agents
Humectant		Emulsion Stabilizers	
Perfume		Mixed Emulsifiers	
		Humectants	
		Stabilizers	

3. Conclusion

A range of excipients are used in the formulation of semi-solid dosage forms, including creams, ointments, pastes, and gels, to give them specific properties, characteristics and quality related attributes. Finding the

right excipient to formulate a optimized semisolid dosage form can be a challenge, in which excipients can be incorporated in formulation of semisolid dosage form can be either to assist in the manufacture of the system or it can be either protect, support or enhance stability, bioavailability or patient acceptability or it can be used to assist in the identification of the product or it may contribute to its overall safety and effectiveness. Overall, the selection and use of excipients in semi-solid dosage forms is important to ensure that the product has the desired properties and characteristics for the intended use and patient population.

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