CHAPTER 6: SEMI-SOLID DOSAGE FORMS AND TRANSDERMAL DELIVERY SYSTEMS (TDS)

INTRODUCTION

LEARNING OBJECTIVES

The objectives of this unit are to:

- Understand the semi-solid dosage form formulation characteristic
- Understand the transdermal delivery system

LEARNING OUTCOMES

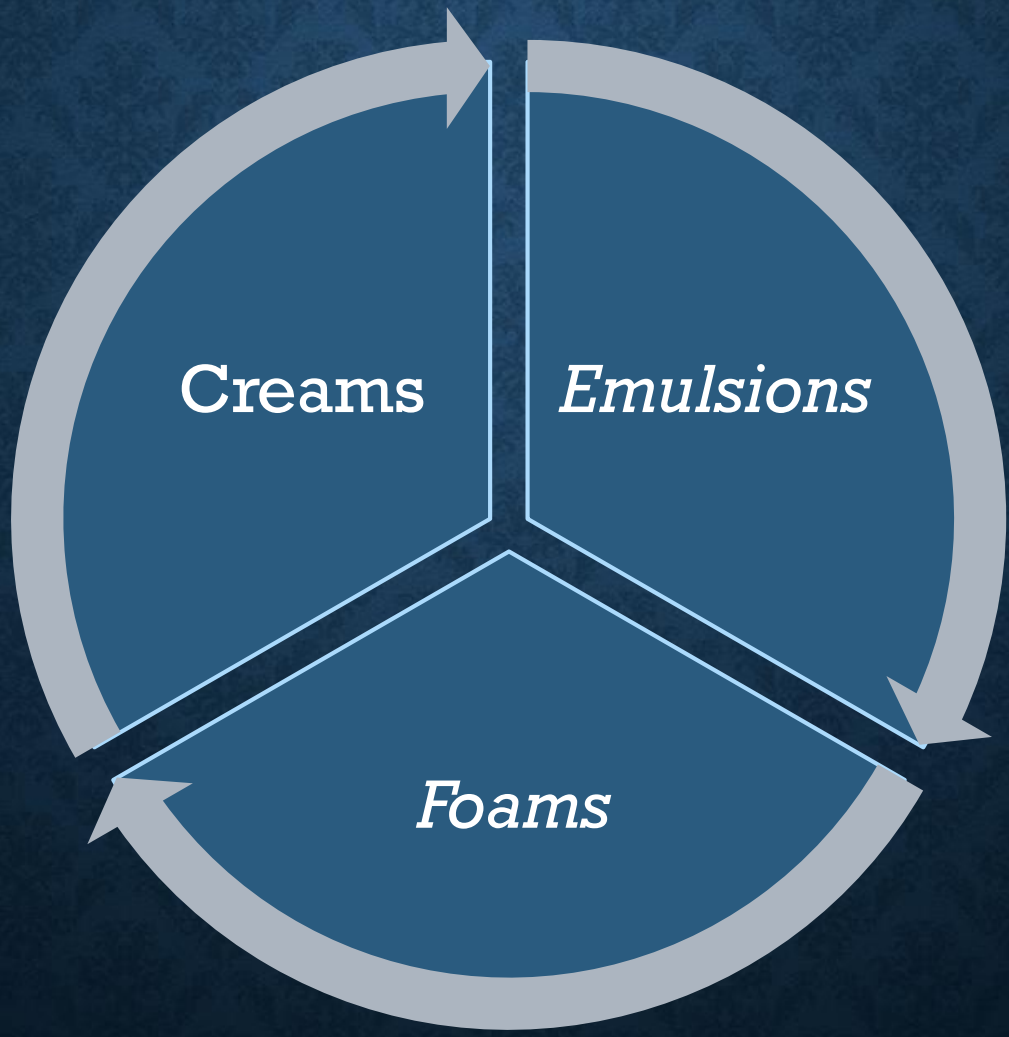
After completing this unit, student should be able to:

- Identify the creams and gels material and formulation design.
- Explain Transdermal drug delivery systems.
- Describe Quality control testing on finished product.

CHAPTER 6: SEMI-SOLID DOSAGE FORMS AND TRANSDERMAL SYSTEMS OINTMENTS

6.1: CREAMS AND GELS MATERIAL AND FORMULATION DESIGN

TYPES OF CREAMS MATERIAL



WHAT IS CREAM?

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

WHAT IS EMULSIONS?

- Emulsions are viscid, multiphase systems in which one or more liquids are dispersed throughout another immiscible liquid in the form of small droplets.
- When oil is the dispersed phase and an aqueous solution is the continuous phase, the system is designated as an oil-in-water emulsion.
- Conversely, when water or an aqueous solution is the dispersed phase and oil or oleaginous materials the continuous phase, the system is designated as a water-in-oil emulsion.
- Emulsions are stabilized by emulsifying agents that prevent coalescence, the merging of small droplets into larger droplets, and, ultimately, into a single separated phase.

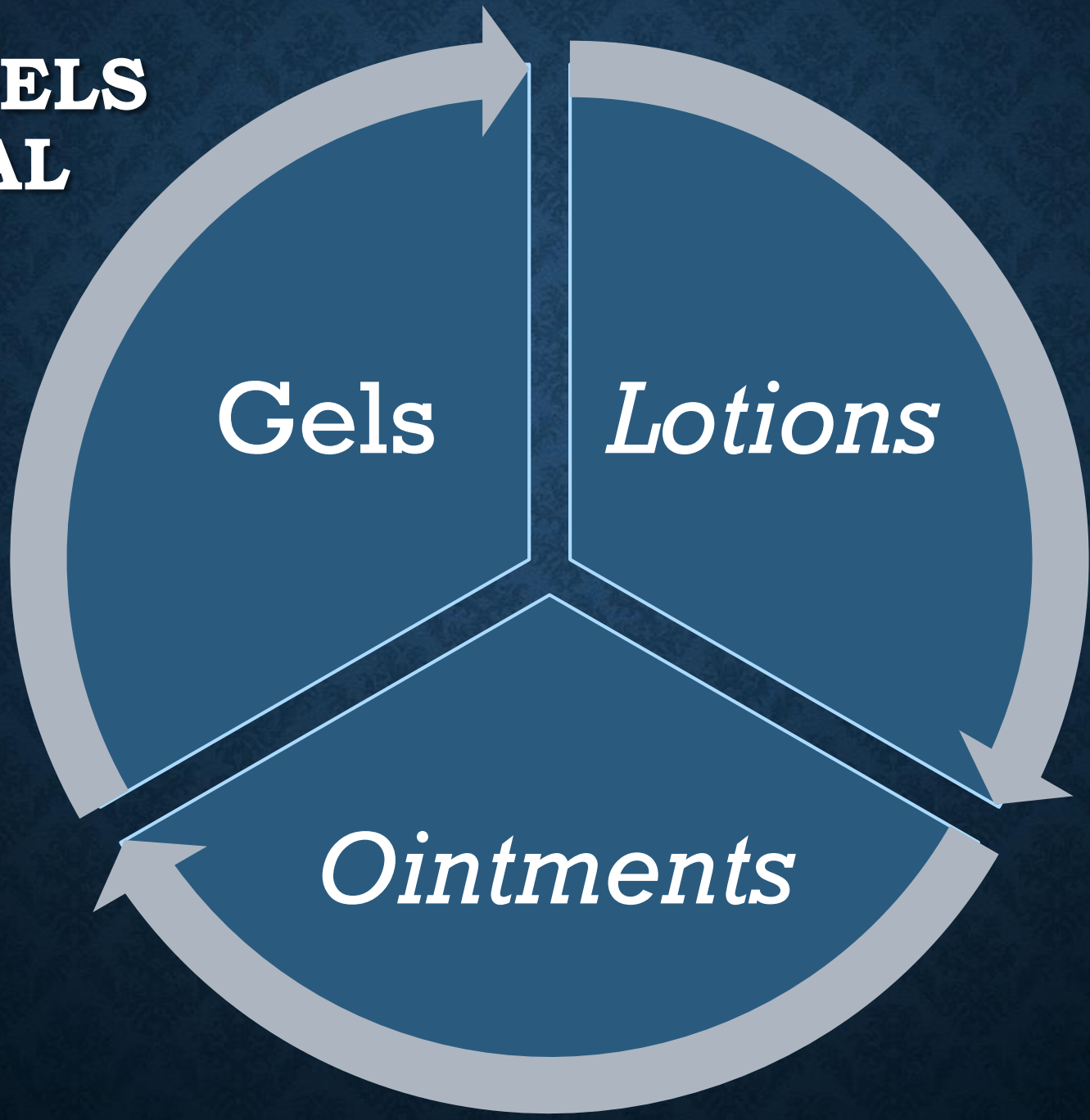
WHAT IS EMULSIONS?

- Emulsifying agents (surfactants) act by concentrating at the interface between the immiscible liquids, thereby providing a physical barrier that reduces the tendency for coalescence.
- Surfactants also reduce the interfacial tension between the phases, facilitating the formation of small droplets upon mixing. The term emulsion is not used if a more specific term is applicable, e.g., cream or ointment.

WHAT IS FOAMS?

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

TYPE OF GELS MATERIAL



WHAT IS GELS?

- Gels (sometimes called Jellies) are semisolid systems consisting of either suspensions composed of small inorganic particles or large organic molecules interpenetrated by a liquid.
- When the gel mass consists of a network of small discrete particles, the gel is classified as a two-phase system (e.g., Aluminum Hydroxide Gel, USP).
- In a two-phase system if the particle size of the dispersed phase is relatively large, the gel mass is sometimes referred to as a magma (e.g., Bentonite Magma, NF). Both gels and magmas may be thixotropic, forming semisolids after standing and becoming liquid when agitated. They should be shaken before use to ensure homogeneity and should be labeled to that effect. Single-phase gels consist of organic macromolecules uniformly distributed throughout a liquid with no apparent boundary between the dispersed macromolecule and liquid.

WHAT IS LOTIONS?

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

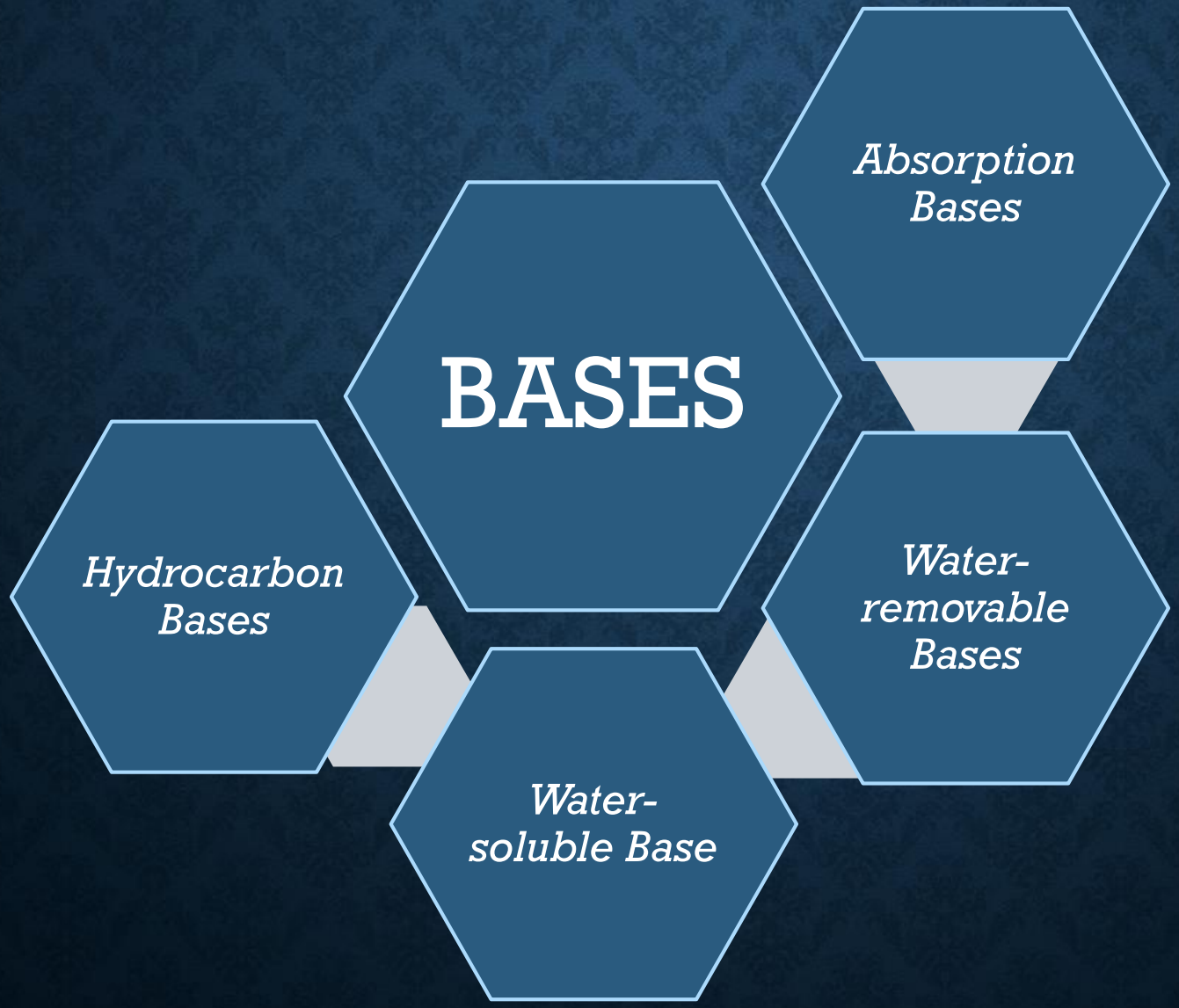
WHAT IS OINTMENTS?

- Ointments are semisolids intended for external application to the skin or mucous membranes.
- They usually contain less than 20% water and volatiles and more than 50% hydrocarbons, waxes, or polyols as the vehicle.
- Ointment bases recognized for use as vehicles fall into four general classes:
    1. hydrocarbon bases,
    2. absorption bases,
    3. water-removable bases,
    4. water-soluble bases.
- Each therapeutic ointment possesses as its base one of these four general classes.

OPHTHALMIC OINTMENTS

- Ophthalmic ointments are semisolids for application to the eye.
- Special precautions must be taken in the preparation of ophthalmic ointments.
- They are manufactured from sterilized ingredients under rigidly aseptic conditions, must meet the requirements under sterility Tests, and must be free of large particles.
- The medicinal agent is added to the ointment base either as a solution or as a micronized powder.

TYPES OF OINTMENTS BASES



HYDROCARBON BASES

- Hydrocarbon bases, known also as "oleaginous ointment bases," are represented by White Petrolatum and White Ointment (both USP).
- Only small amounts of an aqueous component can be incorporated into these bases. Hydrocarbon bases serve to keep medicaments in prolonged contact with the skin and act as occlusive dressings.
- These bases are used chiefly for their emollient effects and are difficult to wash off. They do not "dry out" or change noticeably on aging.

ABSORPTION BASES

- This class of bases may be divided into two groups: the first consists of bases that permit the incorporation of aqueous solutions with the formation of a water-in-oil emulsion (e.g., Hydrophilic Petrolatum and Lanolin, both USP), and the second group consists of water-in-oil emulsions that permit the incorporation of additional quantities of aqueous solutions (Lanolin, USP). Absorption bases also are useful as emollients.

WATER REMOVABLE BASES

- Water-removable bases are oil-in-water emulsions (e.g., Hydrophilic Ointment,USP), and are more correctly called "creams".
- They also are described as "water-washable" because they may be readily washed from the skin or clothing with water, an attribute that makes them more acceptable for cosmetic purposes.
- Some medicaments may be more effective in these bases than in hydrocarbon bases.
- Other advantages of the water removable bases are that they may be diluted with water and that they favor the absorption of serious discharges in dermatological conditions.

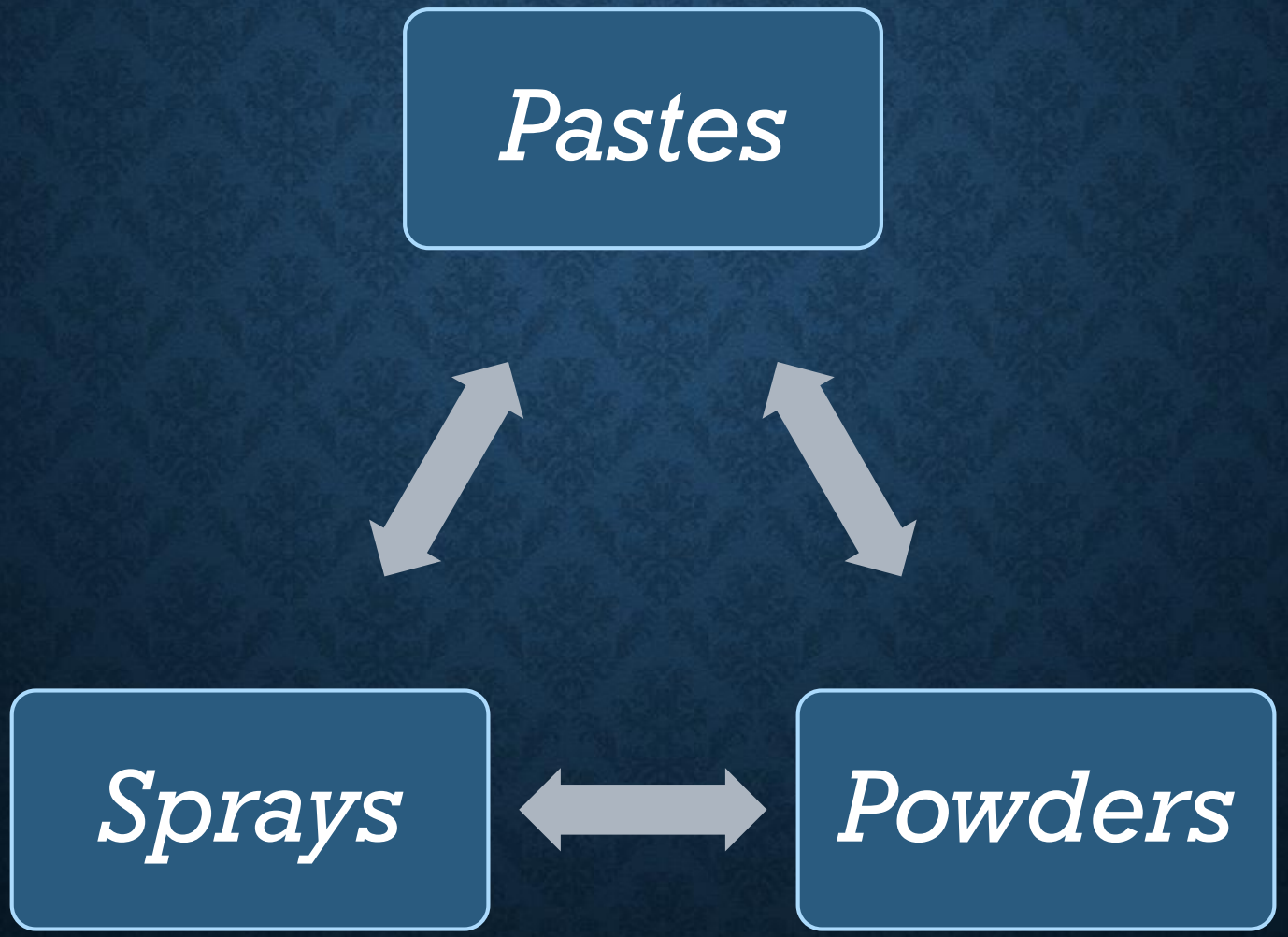
WATER SOLUBLE BASES

- This group of so-called "grease-less ointment bases" comprises water-soluble constituents.
- Polyethylene Glycol Ointment, NF is the only pharmacopeia preparation in this group.
- Bases of this type offer many of the advantages of the water-removable bases and, in addition, contain no water-insoluble substances such as petrolatum, anhydrous lanolin, or waxes.
- They are more correctly called Gels

CHOICE OF BASE

- The choice of an ointment base depends on many factors, such as:
  1. The action desired.
  2. The nature of the medicament to be incorporated.
  3. Its bioavailability and stability.
  4. The requisite shelf life of the finished product.
- In some cases, it is necessary to use a base that is less than ideal in order to achieve the stability required.
- Drugs that hydrolyze rapidly, for example, are more stable in hydrocarbon bases than in bases that contain water, even though they may be more effective in the latter.

FORMULATION DESIGN FOR CREAMS & GELS



WHATS IS PASTE?

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

WHAT IS POWDER & SPRAY?

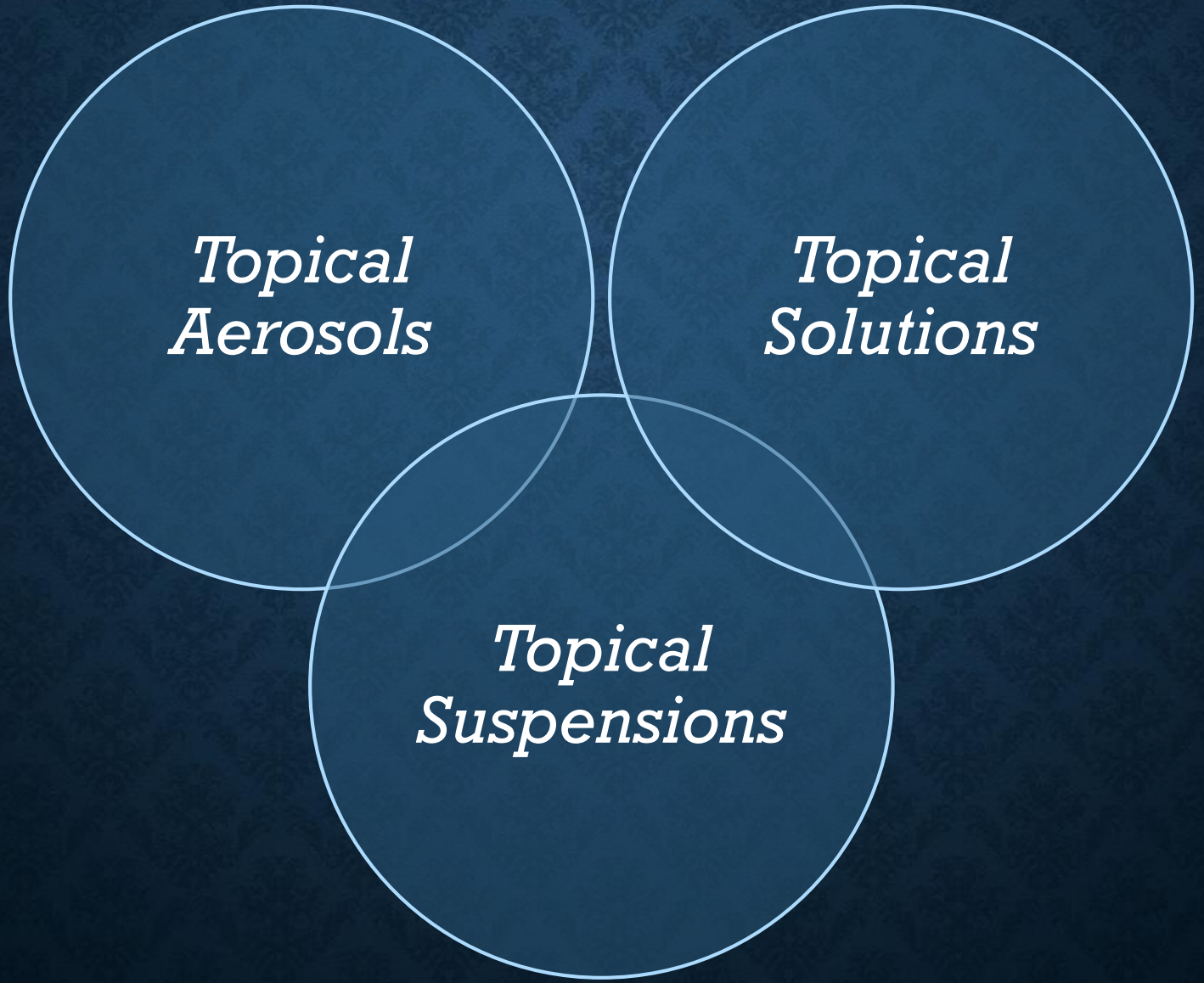
Powders

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

Sprays

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

TYPES OF TOPICAL FORMULATION DESIGN



TYPES OF TOPICAL FORMULATION DESIGN

Topical Aerosols

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

Topical Solutions

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

Topical Suspensions

- Topical suspensions are liquid preparations that contain solid particles dispersed in a liquid vehicle intended for application to the skin.
- Some suspensions labeled as "Lotions" fall into this category.

CHAPTER 6: SEMI-SOLID DOSAGE FORMS AND TRANSDERMAL SYSTEMS OINTMENTS

6.2: TRANSDERMAL DRUG DELIVERY SYSTEMS

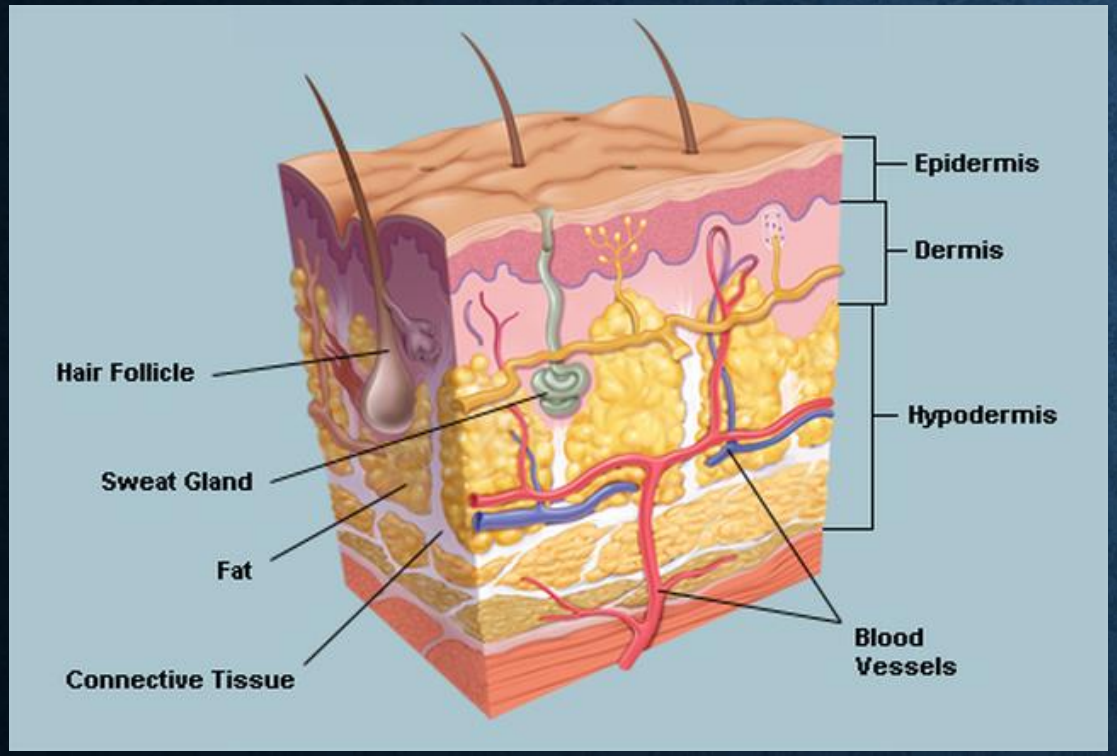
INTRODUCTION

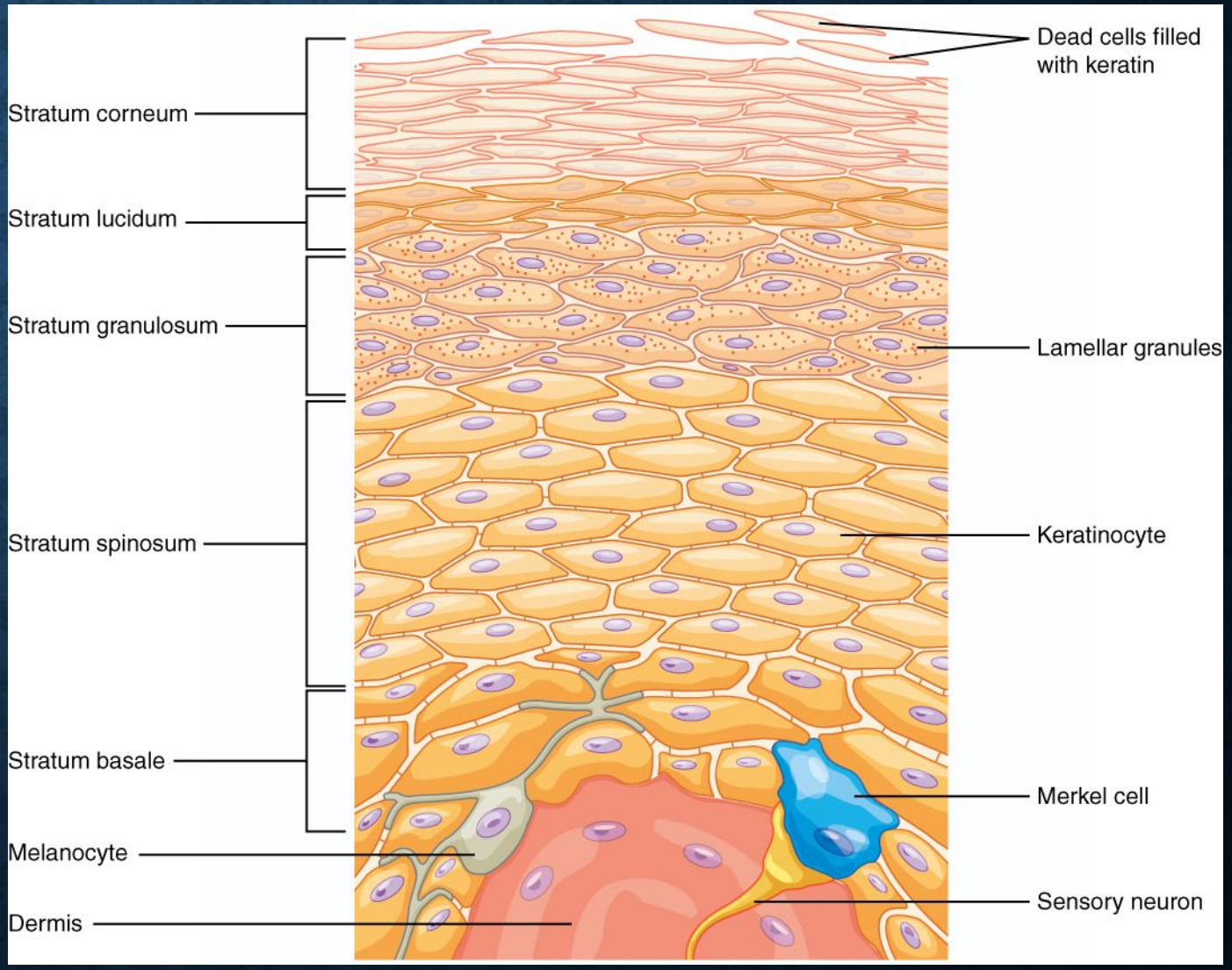
Drug products topically administered via the skin fall into two general categories, those applied for:

1. Local action.

2. Those for systemic effects.

LAYER OF SKIN





INTRODUCTION

- **Local actions** include those at or on the surface of the skin, those that exert their actions on the stratum corneum, and those that modulate the function of the epidermis and/or the dermis. Common products in the former category include creams, gels, ointments, pastes, suspensions, lotions, foams, sprays, aerosols, and solutions. Creams, ointments, and gels generally are referred to as semisolid dosage forms.
- The most common drug products applied to the skin **for systemic effects** are referred to as self-adhering transdermal drug delivery systems (TDS) or transdermal patches. TDS or transdermal patches are physical devices applied to the skin and vary in their composition and method of fabrication. Therefore, they release their active ingredients by different mechanisms.

WHAT IS TDS?

- *Transdermal Delivery Systems*
- Transdermal delivery systems (TDS) are self-contained, discrete dosage forms that, when applied to intact skin, are designed to deliver the drug(s) through the skin to the systemic circulation.
- Systems typically comprise an outer covering (barrier), a drug reservoir that may have a drug release–controlling membrane, a contact adhesive applied to some or all parts of the system and the system/skin interface, and a protective liner that is removed before the patient applies the system.

WHAT IS TDS?

- The dose of these systems is defined in terms of:

1. The release rate of the drug(s) from the system and
2. Surface area of the patch and
3. Expressed as mass per unit time for a given surface area.

- With these drug products, the skin typically is the rate-controlling membrane for the drug input into the body. The total duration of drug release from the system and system surface area may also be stated.

WHAT IS TDS?

- TDS work by diffusion: The drug diffuses from the drug reservoir, directly or through the rate-controlling membrane and/or contact adhesive if present, and then through the skin into the general circulation.
- Typically, modified-release systems are designed to provide drug delivery at a constant rate so that a true steady-state blood concentration is achieved and maintained until the system is removed.
- Following removal of the system, blood concentration declines at a rate consistent with the pharmacokinetics of the drug.

CHAPTER 6: SEMI-SOLID DOSAGE FORMS AND TRANSDERMAL SYSTEMS OINTMENTS

6.3: QUALITY CONTROL TESTING

CATEGORIES OF QUALITY CONTROL TESTING

Product quality tests

- Product quality tests are performed to assess attributes such as assay, identification, content uniformity, pH, microbial limits, and minimum fill and are part of the compendia monograph.

Product performance tests

- Product performance tests are conducted to assess drug release from the finished dosage form.

* This quality control testing are performed with drug products to provide assurances of batch-to-batch quality, reproducibility, reliability, and performance.

QUALITY CONTROL TESTING

- Topical dosage forms include solutions (for which release testing is not indicated), collodion, suspensions, emulsions (e.g., lotions), semisolids (e.g., foams, ointments, pastes, creams, and gels), solids (e.g., powders and aerosols), and sprays.
- The physical characteristics of these dosage forms vary widely. Therefore, the in vitro release test for those products also may differ significantly and may require different types of apparatus.
- At present, a product performance test exists only for semisolid formulations, specifically creams, ointments, and gels. That test employs the vertical diffusion cell (VDC) system. The VDC system is simple to operate and yields reliable and reproducible results when employed by properly trained laboratory personnel.

QUALITY CONTROL TESTING

- The International Conference on Harmonization (ICH) Guidance Q6A (available at www.ich.org) recommends specifications (tests, procedures, and acceptance criteria) to ensure that commercialized drug products are safe and effective at release and during shelf life.
- Tests that are universally applied to ensure safety and efficacy include description, identification, assay, and impurities.

RECOMMENDS SPECIFICATIONS

Description

- A qualitative description of the dosage form should be provided. The acceptance criteria should include the final acceptable appearance. If color changes during storage, a quantitative procedure may be appropriate. It specifies the content or the label claim of the article.

Identification

- Identification tests should establish the identity of the drug or drugs present in the article and should discriminate between compounds of closely related structure that are likely to be present. Identity tests should be specific for the drug substances. The most conclusive test for identity is the infrared absorption spectrum. If no suitable infrared spectrum can be obtained, other analytical techniques can be used. Near infrared (NIR) or Raman spectrophotometric methods also could be acceptable as the sole identification method of the drug product formulation. Identification solely by a single chromatographic retention time is not regarded as specific. However, the use of two chromatographic procedures for which the separation is based on different principles or a combination of tests in a single procedure can be acceptable.

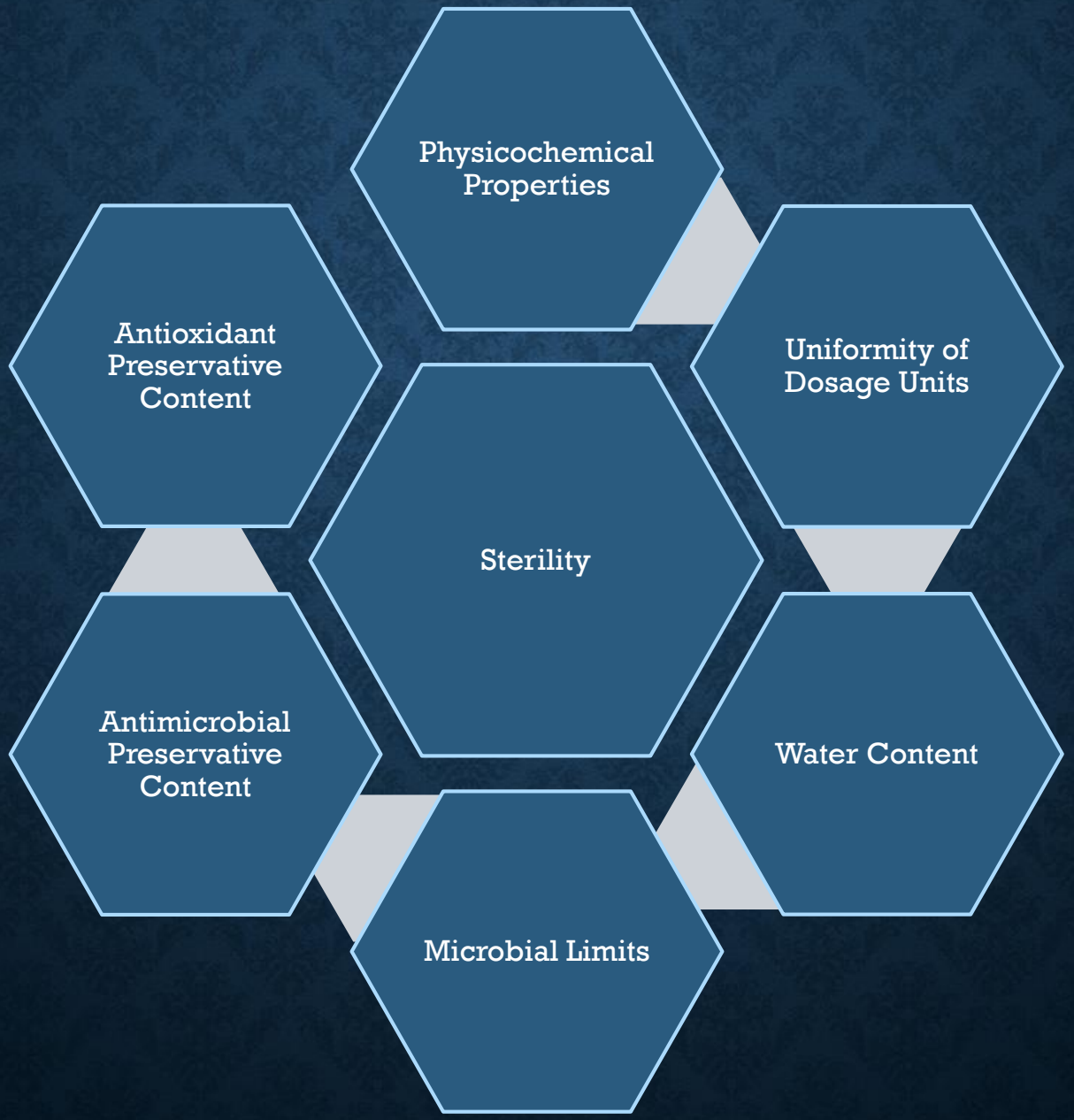
Assay

- A specific and stability-indicating test should be used to determine the strength (content) of the drug product. In cases when the use of non- specific assay is justified, e.g., Titrimetric, other supporting analytical procedures should be used to achieve overall specificity. A specific procedure should be used when there is evidence of excipient interference with the nonspecific assay.

Impurities

- Process impurities, synthetic by-products, and other inorganic and organic impurities may be present in the drug substance and excipients used in the manufacture of the drug product. These impurities are controlled by the drug substance and excipients monographs. Organic impurities arising from the degradation of the drug substance and those arising during the manufacturing process of the drug product should be monitored. In addition to the universal tests listed above, the following tests may be considered on a case-by-case basis

IMPURITIES


Physicochemical Properties
Antioxidant Preservative Content
Uniformity of Dosage Units
Sterility
Antimicrobial Preservative Content
Water Content
Microbial Limits

EXPLAINATION

Physicochemical Properties

- These are properties such as pH, Viscosity, and Specific Gravity.

Uniformity of Dosage Units

- This test is applicable for TDS and for dosage forms packaged in single-unit containers. It includes both the mass of the dosage form and the content of the active substance in the dosage form. The test can be performed by either content uniformity or weight variation

Water Content

- A test for water content should be included when appropriate.

Microbial Limits

- The type of microbial test(s) and acceptance criteria should be based on the nature of the drug substance, method of manufacture, and the intended use of the drug product.

EXPLAINATION

Antimicrobial Preservative Content

- Acceptance criteria for preservative content in multi dose products should be established. They should be based on the levels of antimicrobial preservative necessary to maintain the product's microbiological quality at all stages throughout its proposed usage and shelf life.

Antioxidant Preservative Content

- If antioxidant preservatives are present in the drug product, tests of their content normally should be determined.

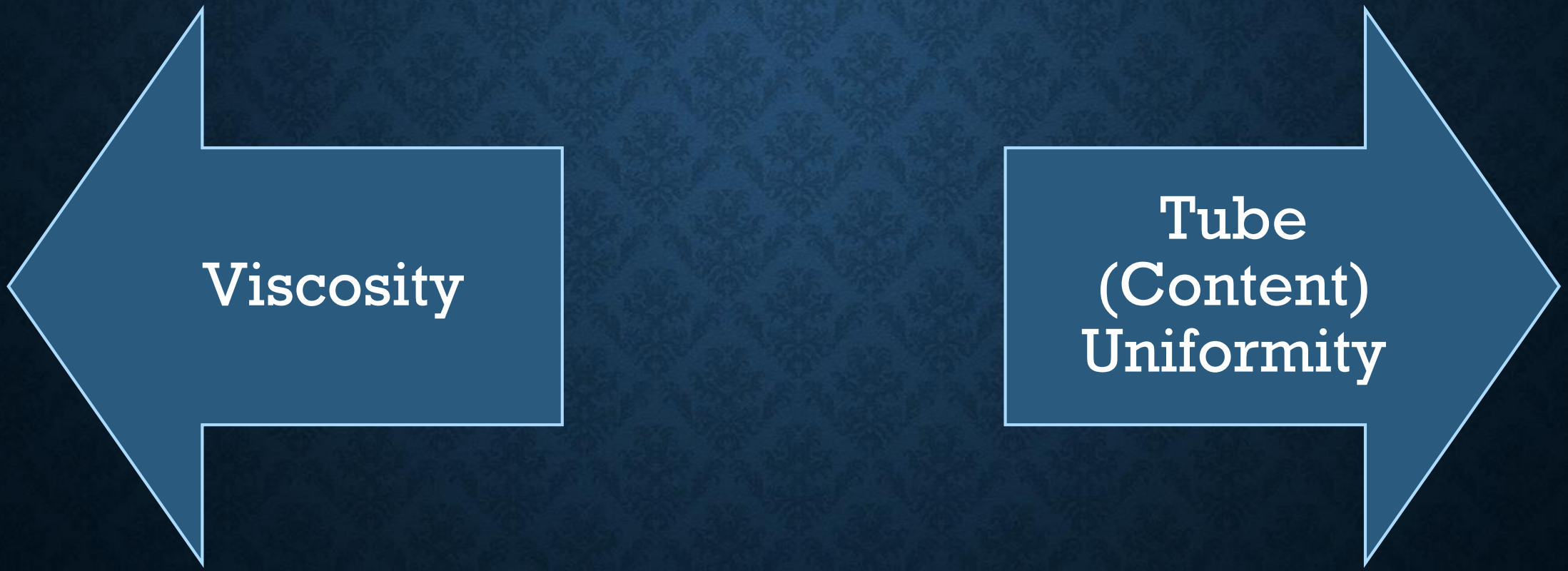
Sterility

- Depending on the use of the dosage form, e.g., ophthalmic preparations, sterility of the product should be demonstrated as appropriate

QUALITY CONTROL TESTING

- General product quality tests such as identification, assay, content uniformity (uniformity of dosage units), impurities, pH, water content, microbial limits, antimicrobial preservative content, antioxidant preservative content, and sterility should be performed for topical drug products as described before.
- In addition, specific tests for topical dosage forms, as described below, also should be conducted.

TESTS FOR TOPICAL DOSAGE FORMS



VISCOSITY

- Rheological properties such as viscosity of semisolid dosage forms can influence their drug delivery.
- Viscosity may directly influence the diffusion rate of drug at the microstructural level.
- Yet semisolid drug products with relatively high viscosity still can exhibit high diffusion rates when compared to semisolid products of comparatively lower viscosity.
- These observations emphasize the importance of rheological properties of semisolid dosage forms, specifically viscosity, on drug product performance.
- Depending on its viscosity, the rheological behavior of a semisolid drug product may affect its application to treatment site(s) and consistency of treatment and thus the delivered dose. Therefore, maintaining reproducibility of a product's flow behavior at the time of release is an important product manufacturing control to maintain and demonstrate batch-to-batch consistency. Most semisolid dosage forms, when sheared, exhibit non- Newtonian behavior

VISCOSITY

- Structures formed within semisolid drug products during manufacturing can show a wide range of behaviors, including shear thinning viscosity, thixotropic, and structural damage that may be irreversible or only partially reversible. In addition, the viscosity of a semisolid dosage form is highly influenced by such factors as the inherent physical structure of the product, product sampling technique, sample temperature for viscosity testing, container size and shape, and specific methodology employed in the measurement of viscosity.
- A variety of methods can be used to characterize the consistency of semisolid dosage forms, such as penetrometry, viscometry, and rheometry. With all methods significant attention is warranted to the shear history of the sample. For semisolids, viscometer geometries typically fall into the following categories: concentric cylinders,cone-plates, and spindles.
- Concentric cylinders and spindles typically are used for more fluid, flow able semisolid dosage forms. Cone-plate geometries are more typically used when the sample size is small or the test samples are more viscous and less flow able. When contemplating what viscosity parameter(s) to test, one must consider the properties of the semisolid drug product both “at rest” (in its container) and as it is sheared during application.

VISCOSITY

- The rheological properties of the drug product at rest can influence the product's shelf life, and its properties under extensive shear can influence its spread ability and, therefore, its application rate that will affect the safety and efficacy of the drug product. Further, although it is necessary to precisely control the temperature of the test sample during the viscosity measurement, one should link the specific choice of the temperature to the intended use of the drug product (e.g., skin temperature for external application effects).
- Because semisolid dosage forms frequently display non-Newtonian flow properties, formulators should give close attention to the shear history of the sample being tested, such as the shear applied during the filling operation, shear applied dispensing the product from its container, and shear introducing the sample into the viscometer. The point of reemphasizing this aspect is that considerable variability and many failures to meet specifications can be directly attributed to a lack of attention to this detail rather than a change of viscosity (or flow properties) of the drug product.

TUBE (CONTENT) UNIFORMITY

- Tube uniformity is the degree of uniformity of the amount of active drug substance among containers, i.e., tubes containing multiple doses of the semisolid topical product. The uniformity of dosage is demonstrated by assay of top, middle, and bottom samples (typically 0.25–1.0 g) obtained from a tube cut open to withdraw respective samples for drug assay.

THANK YOU

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