UNIT-2

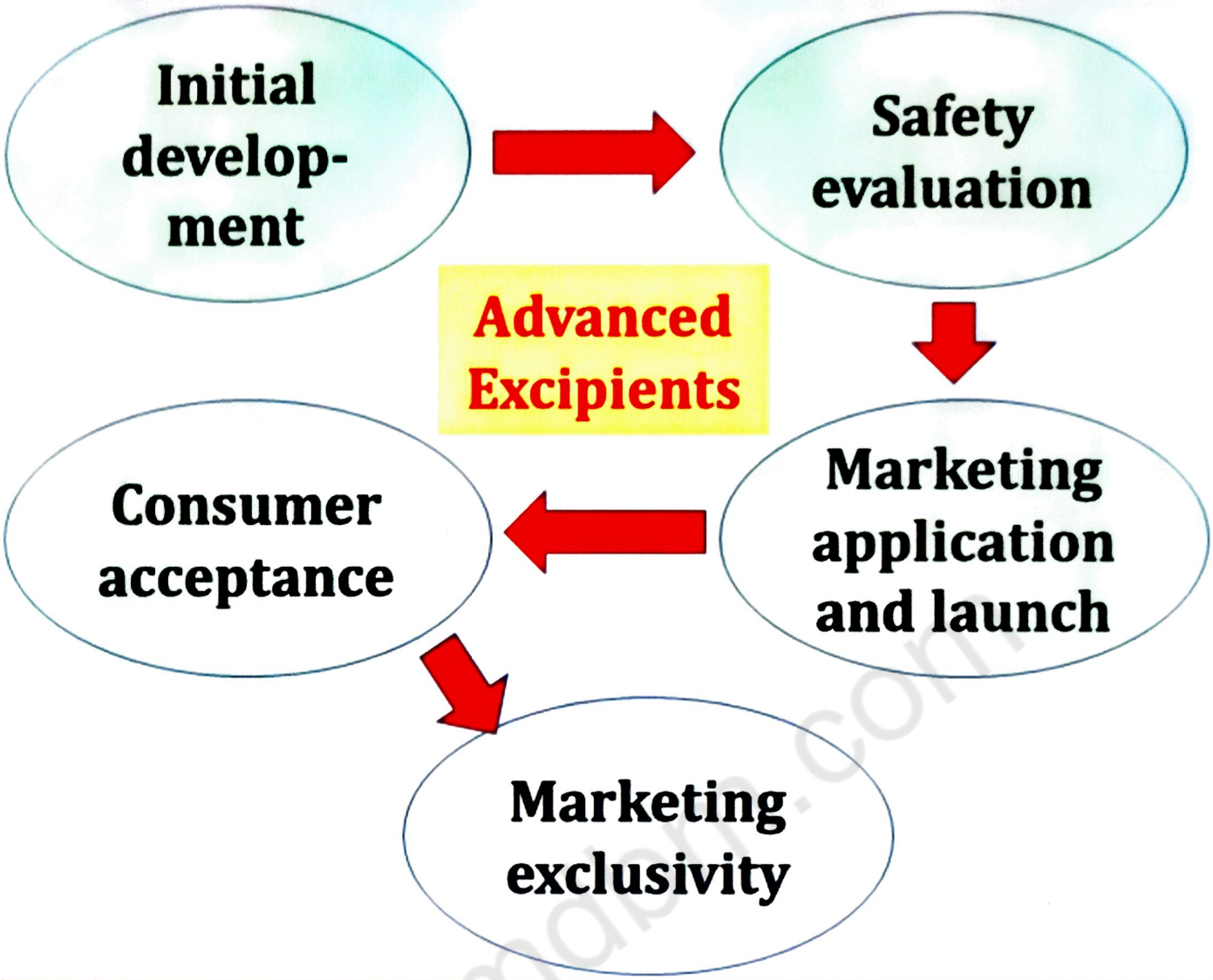
Advanced study of Pharmaceutical Excipients-I

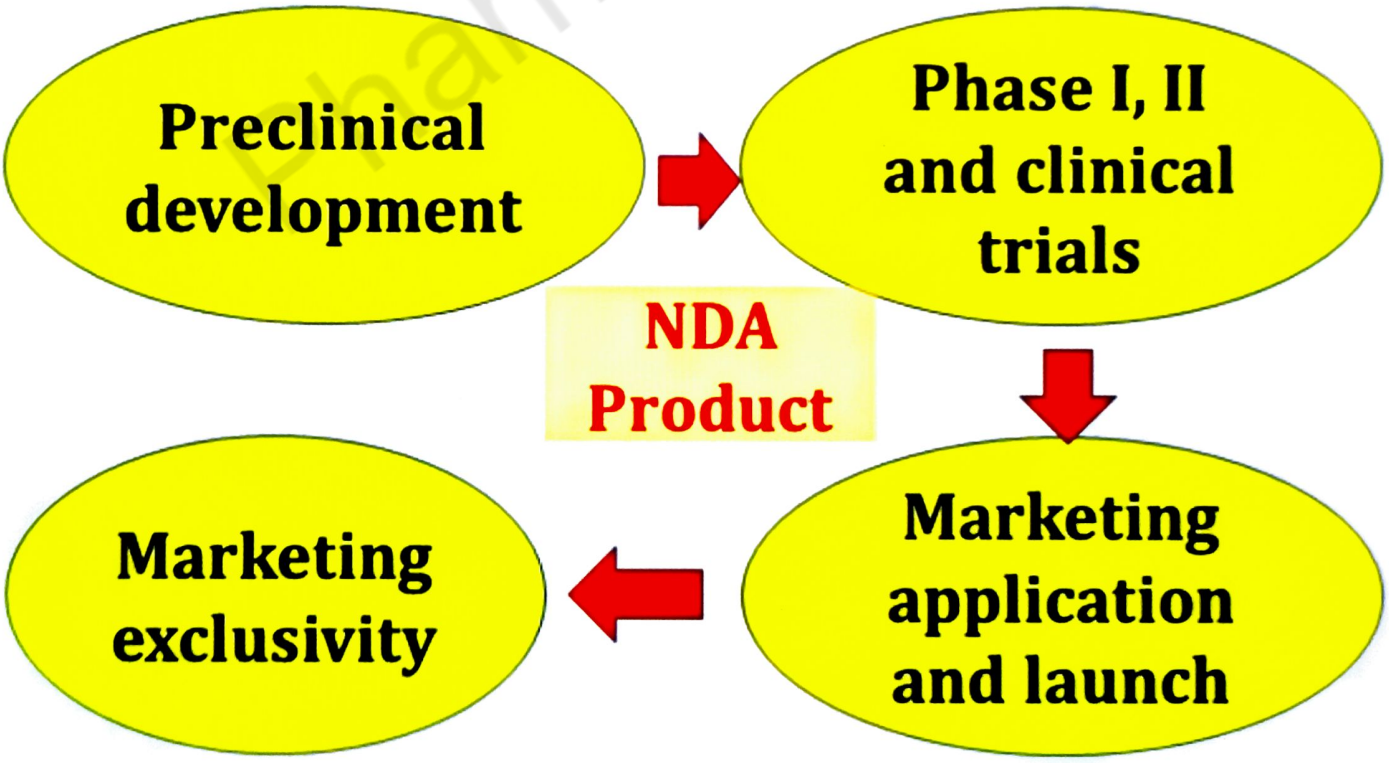
Points to be covered in this topic

- Pharmaceutical excipients in pharmaceutical product development
- Solvents and solubilizers
- Cyclodextrins
- Non - ionic surfactants
- Polyethylene glycols and sorbitol's
- Suspending and emulsifying agents
- Semi solid excipients

❑ AN ADVANCED STUDY OF PHARMACEUTICAL EXCIPIENTS IN PHARMACEUTICAL PRODUCT DEVELOPMENT

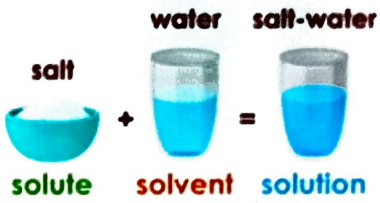
- Pharmaceutical excipients are chemicals used in the **manufacturing process or included in the dosage form of a completed pharmaceutical** product but are not pharmacologically active drugs or prodrugs.
- Pharmaceutical excipients are described in **USP 33** as **"Substances other than the active pharmaceutical ingredient that have been appropriately evaluated for safety and are intentionally included in a drug delivery system".**
- These materials are quite diverse in terms of their origin, chemistry, physicochemical characteristics, and utility. **Sugars, starches, or modified starches, minerals, cellulose and its derivatives, water, fats and oils, and other solvents are the most often used excipients.** These ingredients have all been used for a very long time in **pharmaceutical and cosmetic formulations**. It is now understood that excipients play specific functional roles in pharmacological dose forms.
- These are key ingredients that play a crucial part in formulations, **enabling distribution, enhancing manufacturability, stabilizing the API, etc.**
- In the development of pharmaceuticals, choosing the optimal excipients for a certain functionality is crucial. **New excipients are required as new pharmaceuticals become more difficult to create in order to facilitate their delivery, production, and development.**


Initial develop-ment
Safety evaluation
Advanced Excipients
Marketing application and launch
Consumer acceptance
Marketing exclusivity


Preclinical development
Phase I, II and clinical trials
NDA Product
Marketing application and launch
Marketing exclusivity

❑ Solvents and solubilizers

Solvents
are the component of a solution present in the greater or greatest amount, with other substances in lesser amounts defined as the solute or solutes.
Solutes dissolve into solvents to form solutions.



- A component of **pharmaceutical goods** intended for internal or exterior use that serves as a carrier or diluent in which liquids, semi-solids, or solids are dissolved or suspended is referred to as a solvent. Solvents are **chemical substances** that may **dissolve, suspend, or extract** other materials—typically without undergoing any chemical change in either the solvents or the other materials—and are utilized in thousands of medicinal products.
- They can be either **organic** (the solvent contains carbon as part of its constitution, like rubbing alcohol) or **inorganic** (the solvent does not contain carbon), like water.
- Many medicinal preparations wouldn't work if the solvents weren't there.
- Solvents are extremely flexible and can be created or combined to create goods with the best performance while also meeting highly precise criteria. The most common carrier in **medicinal goods is solvent**. A vehicle is a carrier or inert material that is utilized as a solvent (or diluent) in the formulation and/or administration of the API.
- Depending on their purpose and delivery method, vehicles come in a wide variety of shapes and sizes. The pharmaceutical delivery system may be **oily, watery, solid, or semi-solid**. Drug molecules that are poorly water-soluble can be difficult to effectively administer in vivo due to solubility limitations.
- **Water, alcohol, acetic acid, propylene glycol, oils, ethyl acetate, syrups, and others are typical examples of solvents. Co-solvents make solutes more soluble in solvents.**

- **Co-solvent systems function by lowering the interfacial tension between hydrophobic solutes and primarily aqueous solutions.** Ethanol, sorbitol, glycerin, propylene glycol, and other substances are examples of cosolvents.
- There is a wide range of solubilizers that can be categorized into **water-soluble organic solvent, water-insoluble organic solvents, triglycerides, surfactants, phospholipids, semi- solids and cyclodextrins.**

➢ Water-Soluble Organic Solvents

- In pharmaceutical formulations, **PEG 400, ethanol, propylene glycol, glycerin, and transcutol HP are examples of organic solvents that are water-soluble.**
- **Transcutol, a potent solubilizer**, is a refined form of the solvent diethylene glycol monomethyl ether. Prescription and over-the-counter liquid-filled capsules frequently contain PEG 400. **PEG 400-containing mixtures are also often utilized, such as those including propylene glycol, medium-chain triglycerides, peppermint oil, and the ternary compound of PEG 400, propylene glycol, and 8% ethanol.**
- The **amount of PEG 400 can have an impact on oral bioavailability since more PEG 400 reduces the time that food travels through the small intestine.**

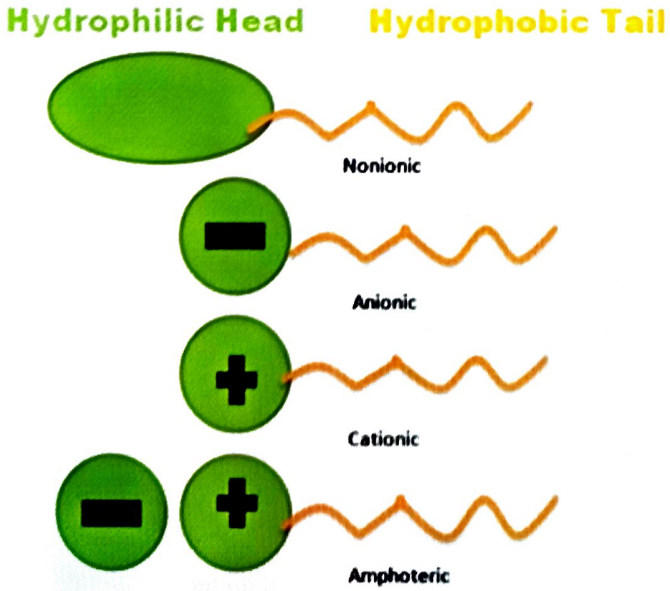
➢ Water-Insoluble Organic Solvents

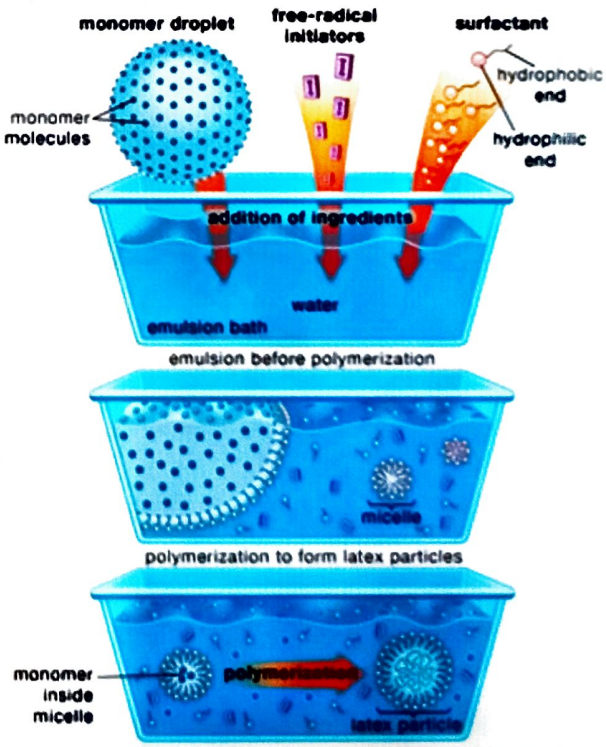
- When solid wet granulation, solid dry granulation, or water-soluble liquid in a capsule do **not give the necessary bioavailability, lipid-based solvents are used for medications that are water-insoluble.**

- Additionally, they can be taken with medications like **indomethacin, farnesil, teprenone, tocopherol nicotinate, etc.** that are themselves oily substances. **Oleic acid, vitamin E, medium-chain mono- and diglycerides, long-chain triglycerides (such as those found in peanut, corn, soybean, sesame, olive, peppermint, and castor oils), medium-chain triglycerides made from coconut and palm seed oils, mono- and diesters of propylene glycol, and monoesters of glycerol are a few examples of water-insoluble solvents.**
- At normal temperatures, **oleic acid is an almost colourless liquid.**
- At room temperature, **vitamin E is an oily liquid and an antioxidant.**

➢ Surfactants

- Surfactants are substances that create **self-assembled molecular clusters called micelles in a solution (water or oil phase) and adsorb to the interface between a solution and a different phase (gases/solids).**
- Cremophors, which are complex combinations of hydrophobic and hydrophilic molecules, are frequently used in conjunction and are particularly successful at soluble highly hydrophobic medicines.





Solvents in Dosage Forms

- As opposed to oily bases found in **creams and gels, such as white petroleum, lanolin, cholesterol, hydro-alcoholic liquids, etc.,** solvents in semi-solid dosage forms include sugar and gum, PEGs, glycerine, gelatin, cocoa butter, and adeps neutralis.
- Oral solutions and solutions put into soft or hard capsules are examples **of solubilized oral formulations**.
- The development of a solubilized formulation in a capsule for oral administration is warranted for a number of reasons, including: increasing the oral bioavailability of a poorly water-soluble drug, a drug that occurs as an oil, a low dosage strength, a drug that has a rapid onset of action by reducing the time for maximum plasma concentration, an increased therapeutic effect by increasing the maximum plasma concentration, maintaining API stability, and reducing the effect of food on oral bioavailability.

❑ Cyclodextrins

- When **first discovered** a century ago, cyclodextrins were first known as **cellulosine.**
- These are starches that have undergone enzymatic modification as a result of the enzyme glucosyltransferase (CGTase) reacting with starch.
- A category of substances known as cyclic oligosaccharides, or cyclodextrins, are composed of **sugar molecules** bonded together in a ring.
- These are **cyclic (a-1,4)-linked oligosaccharides** of a-D-glucopyranose with a hydrophilic outer surface and a moderately hydrophobic core cavity.
- The three naturally occurring cyclodextrins have **cone shapes** and are classified as **α–, β–, or γ–**, respectively, corresponding to six, seven, and eight glucopyranose (sugar ring molecule) units.
- They also **differ in terms of ring size and solubility**.
- Cyclodextrins are molecules with a **ring or torus form**.

- These three naturally occurring cyclodextrins are referred to as Schardinger sugars because F. Schardinger discovered them. **32 units of 1,4-anhydroglucopyranoside** are included in the largest, best-characterised cyclodextrin.
- There is also a poorly understood mixture that contains cyclic oligosaccharides with at least **150 members**. Along with these cyclodextrins that are found naturally, numerous other cyclodextrin derivatives have been created by **aminations, esterifications, or etherification's of the main and secondary hydroxyl groups of the cyclodextrins, depending on the substituent.**
- Cyclodextrin derivatives typically have different solubilities than their parent cyclodextrins.

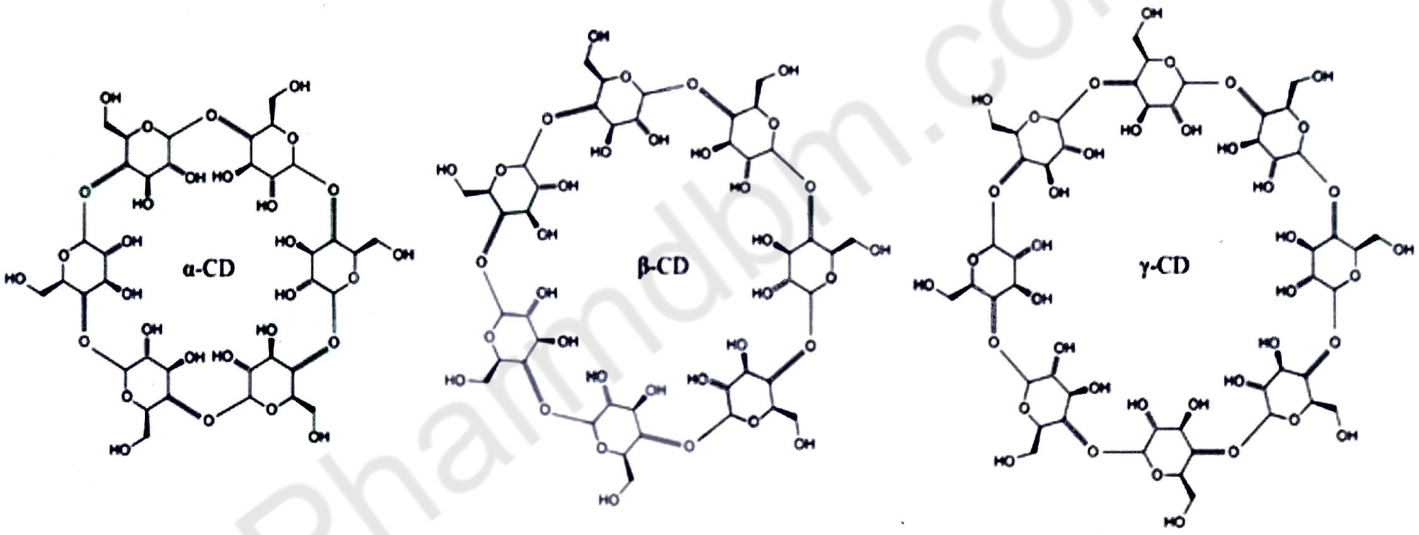


Fig. - Chemical Structure of α, β and γ-Cyclodextrins

Most common cyclodextrin of pharmaceutical interest include; the hydroxypropyl derivatives of **β- and γ-cyclodextrin**, the randomly **methylated β-cyclodextrin, sulfobutylether β-cyclodextrin**, and the so-called branched cyclodextrins such as; **glucosyl β-cyclodextrin**. It is considered that due to steric factors, cyclodextrins having fewer than six glucopyranose units cannot exist. Cyclodextrins containing **9, 10, 11, 12 and 13 glucopyranose units are designated as δ, ε, η and φ cyclodextrin**, respectively.

➢ Properties of Cyclodextrins

(i) **Molecular dimensions of cyclodextrins**

(ii) **Solubility of cyclodextrins**

(iii) **Thermal stability**

➢ Applications of Cyclodextrins

The main **use of cyclodextrins has been as a complexing agent to improve the water solubility of poorly soluble pharmaceuticals and, in a few circumstances, to improve their bioavailability and stability. Cyclodextrins can also be used to prevent drug-drug and drug-excipient interactions, minimize gastrointestinal drug irritation, turn liquid medications into microcrystalline or amorphous powder, and reduce gastrointestinal drug irritation.**

(a) Pharmaceutical industry: The beneficial effects of complexation of drug with cyclodextrin include; **increased solubility of the drug; bioavailability enhancement; drug stabilization to prevent volatilization, oxidation, and degradation due to exposure to light and heat**; elimination or reduction in undesired tastes or odors (taste masking); reduction of irritability; prevention of chemical degradation; directed chemical synthesis; and separation and isolation of various chemicals and material handling benefits.

(b) Food industry: Cyclodextrins are used in **food industry as a stabilizer for flavoring agents and to reduce unpleasant odour and taste of food.**

(c) Cosmetic industry: Cyclodextrins are used as **stabilizers of chemically labile compounds, to obtain prolonged action, to decrease local irritation and to reduce unpleasant odours in cosmetic products.**

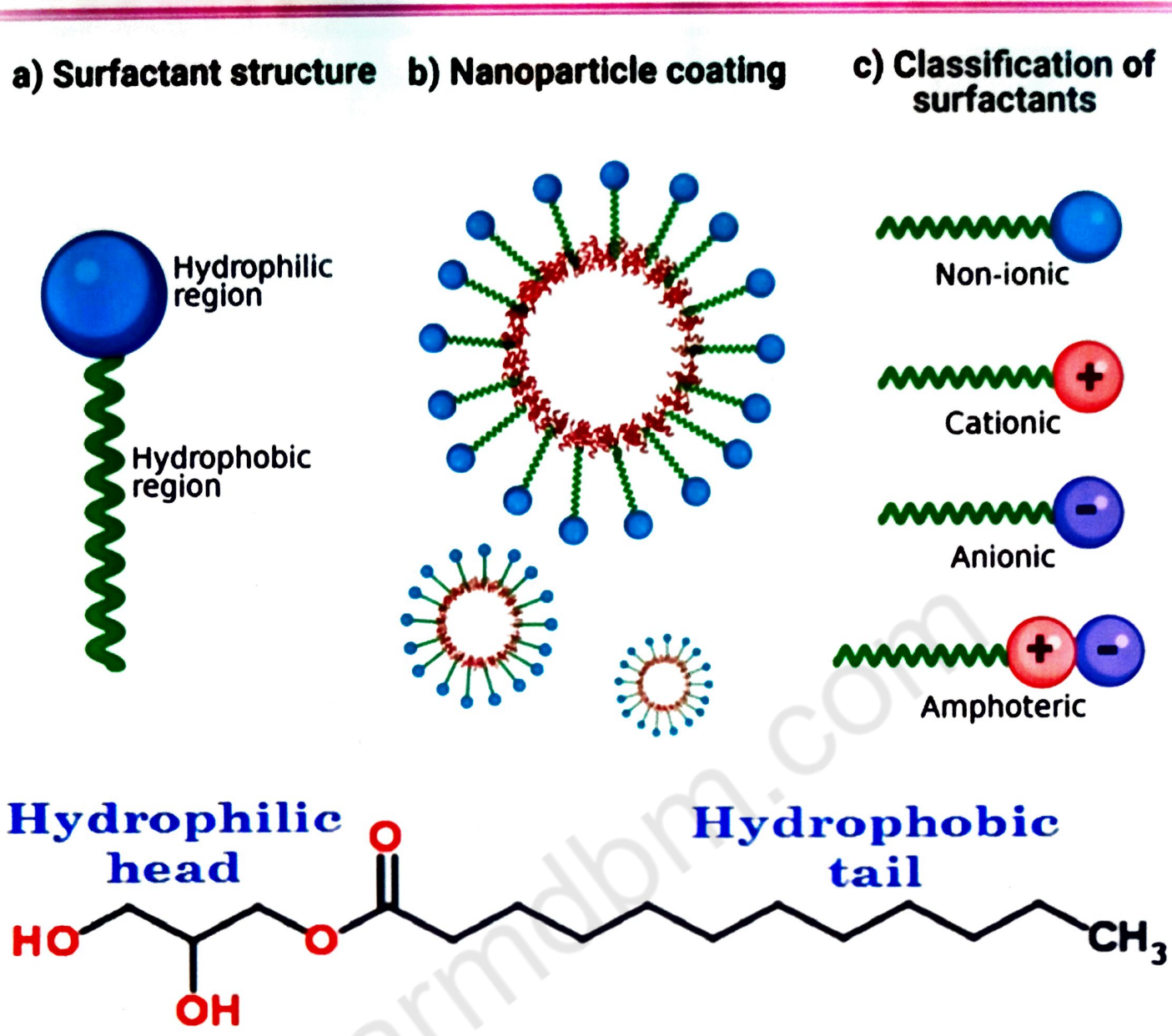
(d) Dispersed systems: Both the **cyclodextrins and their derivatives have been used in dispersed vehicle systems such as emulsions, microcapsules, microspheres, nanospheres, nanocapsules, liposomes and niosomes.** Inclusion complexes of glycerides, fatty acids or fatty alcohols do possess surface activity and this property together with their ability to form aggregates frequently result in formation of dispersed systems.

(e) Process aids: Cyclodextrins can be used as **process aids to remove specific components from a mixture of materials. The components form an inclusion complex with cyclodextrin.** The complex can then be separated from the complex by centrifugation or filtration. The components which have been removed may be discarded or further purified and separated, whereas cyclodextrin is recovered and recycled.

(f) Protection: Interior pan coating compositions are applied to the inner surface of metal containers (pan) to form a protective barrier between the processed materials and the metal surface of the container.

❑ Non - ionic surfactants

- ✓ **Surfactants, sometimes referred to as surface active agents, are a class of molecules that have both sections that love (hydrophilic) and fear (hydrophobic) water.** Because of their **distinctive structure, surfactants play a significant role in many industrial and commercial applications in the pharmaceutical industry.** Some surfactants have an electrical charge on their **hydrophilic moiety, and these substances are classified as non-ionic (having no charge), anionic (having a negative charge), cationic (having a positive charge), and amphoteric (having both a positive and a negative charge).**
- ✓ Nonionic surfactants are those surfactants that do not have any ions. They are the esters of high molecular mass and are generally neutral in nature. In **nonionic surfactants, the water solubility is also relatively**



➢ Classification of Non-Ionic Surfactants

The non-ionic surfactant can be classified as polyol esters, polyoxyethylene esters and sorbitan derivatives (poloxamers). Fatty acid esters of sorbitan (generally referred to as Spans) and their ethoxylated derivatives (generally referred to as Tweens) are perhaps one of the most commonly used non-ionics. The non-ionic surfactants are classified as follows:

(1) Ethoxylated alcohols and alkylphenols:

(a) Ethoxylated linear alcohols

(b) Ethoxylated alkyl-phenols

(c) Ethoxylated thiols

(2) Polyoxyethylene glycol monoethers

(3) Fatty acid esters:

(a) Glycerol esters

(b) Esters of hexitol and cyclic anhydro hexitol:

(i) Sorbitan esters (Span)

(ii) Polysorbates (Tween)

(iii) Poloxamers (Pluronic)

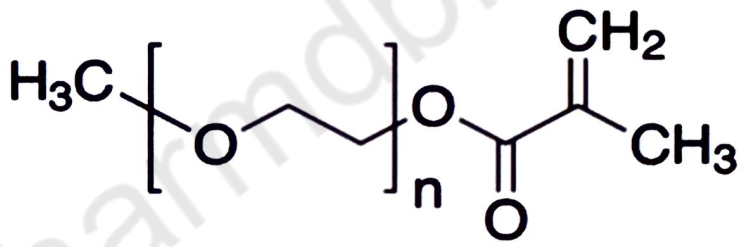
(4) Nitrogenated non ionic surfactants

➢ Applications

1. **Non-ionic surfactants are used for the preparation of niosomes.** Examples polyglycerol alkyl ethers, glucosyl dialkyl ethers, crownethers, ester-linked surfactants polyoxyethylene alkyl ethers, Brij, Spans (sorbitan esters) and Tweens (Polysorbates).
2. The **non-ionic surfactant can improve the therapeutic effect of proteins and peptides by minimizing clearance time from systemic circulation, increase bioavailability and can target and control drug delivery to the site of action.**
3. Non-ionic surfactants are used as **co-emulsifiers for the preparation of the emulsions composed of castor oil, DC-cholesterol or dioleoyl phosphatidylethanolamine.** Example Tween, Span, Brij and pluronic copolymers.
4. Non-ionic biological surfactants are used in **artificial implants, gene transfection, bio membrane, ophthalmology and pharmaceuticals.**
5. They can be used to **enhance dissolution properties of drugs such as spherical agglomerate crystals of felodipine. For example: Inutec SP1.**
6. The non-ionic low ethoxylated monoglyceride can be **used as a skin conditioner, for example, PEG-7 glyceryl cocoate.**
7. They are used to **prepare o/w emulsions and also as a solubilizing agent for volatile oils. Example: Cetomacrogel emulsifying wax.**

❑ Polyethylene glycols (PEGS)

- Polyethylene glycol (PEG), also known as **Macrogol**, is a polyether composed of repeated **ethylene glycol units [-(CH2CH2O),]**.
- PEGS are U.S. FDA approved biodegradable polymers. U.S. FDA's Inactive Ingredient Guide (IG) lists use of **PEGS in oral, topical, and intravenous formulations and it also describes the maximum concentration of PEGS used in that particular composition.**
- **PEGS are available with different degrees of polymerization and activated functional groups. The chemical structure of PEG is (C_2HO) H_2O).**
- The **chemical structures of key PEG derivatives are mainly known by their molecular weights.** PEG follows CAS and Cosmetics, Toiletry and Fragrance Association (CTFA)/ International Nomenclature Cosmetic Ingredient (INCI) nomenclature systems.



➢ Properties

- PEGs are structurally **highly flexible, biocompatible, amphiphilic, devoid of any steric hindrances, and has high hydration capacity.**
- **PEGs with molecular weight 100-700 are liquids at room temperature, between 1000 and 2000 are soft solids, and >2000 are hard crystalline solids with m.p. around 63°C.** High polarity of PEG increases hydrophillicity and thus, enhances water solubility.
- PEG shows **high solubility in most of the organic and inorganic solvents to form a monolayer at air-water interface playing an important role in solubilization and permeation.**
- **PEGS are electrically neutral at all pH with highly active functional groups.**

➢ Applications of PEGs

(1) Solubilizers:

- High polarity of PEG increases the hydrophilicity and hydrophobic interactions with hydrophobic drug for solubilization. This exhibits a high solubility in various organic and inorganic solvents.
- Hydrophobic drugs cannot break the strong lattice structure of water; hence, PEG as a cosolvent facilitates solubilization by decreasing polarity of the solvent system.
- Liquid PEGs can be used as a water miscible solubilizer in oral liquids and parenteral.
- High molecular weight PEGS have been widely used for microencapsulation of drugs. It is also used as solubilizer in ophthalmic/optic drops or in liquid-filled soft gelatin capsules.

(2) Permeation enhancer:

- PEGs shows poor skin penetration due to steric hindrances offered by adsorbed water molecules.
- Non-ionic PEG surfactants and PEG ethers can influence the skin barrier function. Low molecular weight PEG stearate (1-5% w/v) decreases the surface tension and condition the stratum corneum.
- Most of PEGS have decreased penetration and increased skin barrier.

(3) Surface modifier:

- Tethered chains of PEG readily form hydrophilic shell encapsulating hydrophobic core.
- Hydrophilicity is mainly determined by contact angle. Hydrophilic materials decrease the contact angle of hydrophobic material. Surface modification of hydrophobic materials with PEG can offer a hydrophilic hydrated steric barrier, holding the water molecules.
- A large number of water-binding sites are available on PEG chains. Most of the water molecules bind tightly while some are loosely held causing full hydration.

(4) Anti-fouling of medical devices:

- Surface of any implanted medical device **should be smooth, resist activation of host defense system, resist any bacterial adhesion, and allow healthy tissues to grow when placed in host body**. **Infections from protein sorption over period of time and its build-up cause blockage and bacterial growth**. Coating of biomedical devices has been effective to reduce or prevent bio-fouling, for example, reduced attachment of cells or proteins.

(5) Drug targeting:

- PEG conjugated with drug help in **passive targeting to the tumor**. **PEGylation increases The circulating nature of nanoparticles and decreases reticuloendothelial system uptake.**
- This enhances accumulation in tumor via enhanced permeation and retention in infection and inflamed conditions.

(6) Release modifiers:

- Drugs physically entrapped in **PEG matrix are released through diffusion or erosion- controlled mechanism or combination of both.** Water permeates through the shell to the inner core and dissolves the drug followed by diffusion.
- In aqueous solutions, it forms micelles and releases drug in tumor environment.

(7) Binders and plasticizers:

- **In solid dosage formulations, high molecular weight PEGS are used to enhance the effectiveness of tablet binders and impart plasticity to granules.**
- High molecular solid PEGs are used as plasticizers once they are in liquid state either by solubilizing in solvent or by melting. For film **coatings, solid PEGs are**
- **used to give a hydrophilic polished surface in combinations with other film-forming polymers.**

(8) De-aggregation and stabilization:

- **The surface attraction or repulsion property of PEGS depends upon their molecular weights.**

- High molecular weight PEGS mainly induce repulsion, while low molecular weights promote attraction in liquid medium.

(9) Plasma expanders and blood substitutes:

- **High viscosity plasma expanders like PEG-albumin occupies ~1% concentration of plasma.**
- This 1% contributes to a plasma viscosity of ~1.3 cP, marginally larger than viscosity of normal plasma. It has shear-thinning properties and is thus, explored in formation of resuscitation fluids.
- This type of fluids helps to **increase microvessel wall shear stress in microcirculation leading to lower expenditure of energy in systemic circulation.**

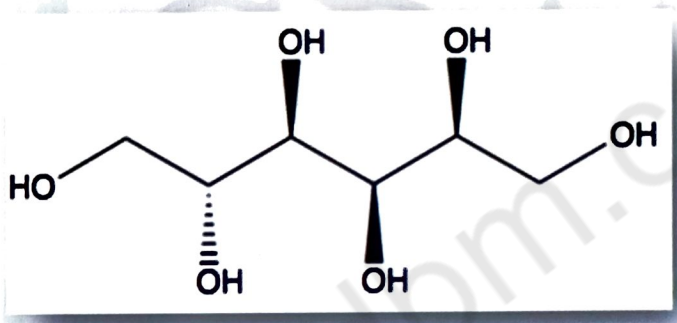
(10) Tissue engineering:

- **PEG hydrogels are easily functionalized with cell adherents and differentiation designs to promote cell functions or to provide a 3D environment for cell proliferation.**
- Thermosensitive PEG gel incorporated with bone morphogenetic protein 2 (BMP-2) supports growth of bone marrow stromal cells which ultimately results in differentiation and deposition of bone matrix.
- **Hydrophilic PEG on injecting undergoes sol-gel transition and fits into size and shape of bone defect.**
- **Derivatives of PEG incorporating cyclicacetals, polycarbonates, and methacrylates are widely used.**

❑ Sorbitol

- **Sugar alcohols are made from the corresponding aldose sugars and are hence referred to as alditols.**
- These **low-molecular-weight, quickly assimilated carbohydrates were created by replacing the aldehyde group with a hydroxyl group.** An excipient used in the formulation of many different **medications is sorbitol, an isomer of mannitol.**

- It is a powdery substance that is **white in colour and odourless.**
- It is a **hydrogenated monosaccharide, often known as sugar alcohol or glucitol.** The liver slowly converts any sorbitol that is ingested into **fructose and glucose**.
- When glucose is reduced, an aldehyde group (-CHO) is changed to a primary alcohol group (-C(OH)H2), resulting in the production of sorbitol. **Fruits also contain sorbitol, which is primarily derived from potato starch. Sorbitol-6-fructose-phosphate 2-dehydrogenase is produced from it.**
- It is used as a **sugar substitute and has about 60% as sweet as sucrose and referred to as a nutritive sweetener because it provides 2.6 kcal/g of dietary energy.**



➢ Applications:

Sorbitol has gained significant attention in the past few years because of its **wide usage as a pharmaceutical excipient and its influence on the disposition and pharmacokinetics of certain drugs.**

(a) Solid dosage form:

- **Sorbitol is extensively used as a diluent in tablet formulations, predominantly useful in chewable tablets owing to its pleasant, sweet taste and cooling sensation.**
- It is also used **as a fast disintegrant in capsules and plasticizer in capsule shells and tablet film coatings.** Sorbitol is used in **sugar-free chewing gum. normally utilized as a sugar substitute as a part of nourishments**
- It is, particularly for diabetics.

(b) Liquid dosage form:

- In oral liquids, **sorbitol is used as a sugar substitute and as a drug stabilizer.**
- It is also often used in **syrups to prevent crystallization around the cap of bottles.**
- It is also used as a **solubility enhancer for drugs such as indomethacin. Sorbitol can be used as a laxative when taken orally or as an enema topically.**

(c) Lyophilized products:

- **Sorbitol is used as a cryoprotectant additive in lyophilized formulation.**
- It is commonly used as a **stabilizing excipient and/or isotonicity agent in both liquid and lyophilized parenteral protein formulations.**

(d) Soft gel capsules:

- Sorbitol is also used in the **manufacture of soft gel capsules to store single doses of liquid medicines.**

(e) Food and cosmetics:

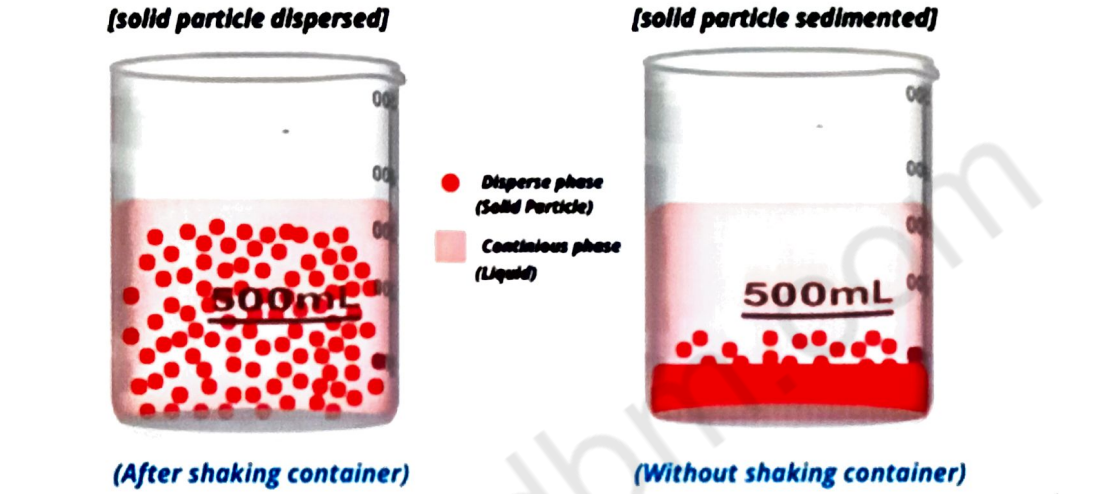
- **Sorbitol is often used in mouthwash and toothpaste as humectant and thickener.** Some transparent gels can be made only with sorbitol, because of its high refractive index.
- In cosmetics, it is regularly utilized as a part of **post-shaving astringent creams, mild soaps and baby shampoos.**
- **It is used in topical formulations as a humectant and skin conditioning agent.**

(f) Bacterial culture media:

- **Sorbitol is used in bacterial culture media to distinguish the pathogenic E. coli O157:H7 from most other strains of E. coli, because it is usually unable to ferment sorbitol.**

❑ Suspending agents

- Suspending agents in pharmaceutical formulations, especially **suspensions, are added to ensure the homogenous distribution of the API, and to ultimately provide physicochemical stability to the formulation.** A number of excipients have been used over the years as suspending agents either for oral, parenteral or topical applications.



- Suspending agents can be of great help in the development of satisfactory dosage forms for insoluble or partly soluble drugs. While selecting the suspending agents, it is important to consider formulation composition, stable pH range, common incompatibility, and color of vehicle, concentration of suspending agent, as well as commercial source and method of preparation.
- One of the properties of a well-formulated suspension is that, it can be easily re- suspended upon moderate agitation or shaking. These agents are **hydrophilic colloid, also called as thickening agents, used to stabilize suspensions. Hydrophilic colloid substances spontaneously form colloidal dispersions with water** because of an affinity between the dispersed particles and the dispersion medium. They **help in lowering the sedimentation of particles in suspension.** They usually prevent caking at the base of a suspension and help to resuspend by agitation.

(1) Gums:

- Gums are materials such as **acacia, tragacanth, Irish moss, algin and its derivatives, pectin, and other products of similar composition, both natural and synthetic.**
- Gums are subject to microbial decomposition and hence require preservatives. Suitable **preservatives include sodium benzoate, p-hydroxybenzoate, alcohol and phenol.**

(a) Guar gum:

- **Guar gum is an odorless, white to yellowish-white powder with a bland taste.**
- It is generally used in **solid dosage forms as a binder or disintegrant, and in liquid oral and topical products as a viscosity-enhancing and stabilizing agent**

(b) Xanthan gum:

- Xanthan gum is a **cream colored or white, odorless, free-flowing fine powder used as a stabilizing agent and as a suspending or viscosity enhancing agent.**
- It is an anionic excipient therefore; its use is **limited when cationic surfactants, polymers and preservatives are used, due to risk of precipitation.**

(c) Acacia:

- **Acacia occurs as round, ovoid, colorless or white powder often used as suspending agent.**
- It is not a good suspending agent but used only because of its protective colloidal property.
- It is useful for preparation of tinctures of resinous materials that precipitate on addition of water.

(d) Tragacanth:

- Tragacanth occurs as thin, white or yellowish white, ribbon like flakes.
- **It forms viscous aqueous solutions.**
- It's thixotropic and pseudo-plastic properties make it better thickening agent than acacia and can be used for externally applied and internally administered formulations.
- **It is stable over pH 4 to 7.5.**

(2) Celluloses:

- Celluloses are so-called synthetic gums which have been obtained from cellulose.
- Their examples include methylcellulose, carboxymethylcellulose, sodium cellulose sulfate, and hydroxyethyl cellulose etc.

(a) Methylcellulose:

- Methylcellulose (MC) occurs as a white, fibrous, hygroscopic powder or as granules.
- **In water, it swells and produces a viscous colloidal suspension**; hence, it is widely used as a suspending agent both in topical and oral formulations.
- The unique feature of MC is its solubility in cold water and insolubility in hot water.
- It has advantage in delaying settling of suspensions and to increase contact time of drugs such as antacids in the stomach. In oral formulation, it is a good substitute to sugar-based syrups

(b) Carboxymethylcellulose sodium:

- Carboxymethylcellulose sodium (CMC-Na) is a hygroscopic, whitish powder or granules.
- It is easily dispersed in water to form colloidal dispersion. CMC-Na is used as a coating, stabilizing and viscosity-increasing agent.
- It is commonly used both in oral and topical formulations.
- It can also be used in wound care and dermatological patches. CMC-Na is soluble in water at all temperatures.

(d) Carbopol:

- Carbopol polymers are offered as fluffy, white, dry powders. Carbopol polymers are high molecular weight, cross linked, acrylic acid based polymers.

(3) Gelatin:

- Gelatin is a **mixture of purified fractions of proteins obtained from animal collagen by partial acidic/alkaline hydrolysis.**
- It has number of amino acids linked together by amide linkage to form linear polymers. Although gelatin is used as a coating agent and gelling agent, it is most commonly used **suspending agent or a viscosity increasing agent.**
- **Gelatin is insoluble in water**, but it **swells in gastric fluid** which helps to release drugs. Therefore, it is used in **the formulations of soft capsules that are designed to dissolve in the stomach.**

(4) Inorganic salts:

The examples of inorganic salt suspending agents are clay, bentonite, aluminum magnesium silicate, aluminum hydroxide, etc.

(a) Clays:

- Clays are **processed and purified products from montmorillonite and similar clay materials.**
- They are **dispersible in water and hydrated to form viscous, thixotropic media**. Their dispersions are opaque, varying from **off-white to tan, not requiring a preservative.**

(b) Bentonite:

- It is a subtype of montmorillonite clays that hydrate readily by absorbing water up to **12 times of their weight particularly at elevated temperatures.**
- The gels formed are thixotropic in nature so, act as good suspending agents. It is used at **2-3% concentration for topical use, for example in Calamine Lotion.**

(c) Veegum:

- Veegum (magnesium aluminum silicate) **dispersions are prepared by slowly adding the material to water with rapid agitation**.
- When veegum is dispersed in hot water, the **final viscosity is appreciably increased.** Veegum is **insoluble flake that disperse and swell readily in water absorbing the aqueous phase into crystal phase**.
- They are used in concentration of 5%, both externally and internally. They are stable at pH 3.5 to 11.

(5) Surfactants:

- **Surfactants also serve as suspending agents that are insoluble and dispersible in water**.
- The examples include both **esters and ethers**, usually non-ionic in nature. The majority have an ester link between the polyoxyethylene group and the hydrophobic group.
- The dispersions are formed by heating the surfactants at **70 °C and adding distilled water above 90 °C to the surfactant with rapid agitation**.

(6) Colloidal silicon dioxide (Aerosol):

- **Colloidal silicon dioxide when dispersed in water forms a 3-D network.**
- It is used up to concentration of **4% for external use and as a thickening agent for non-aqueous suspension.**
- It is obtained from silicon dioxide and is **white non-griffty powder**.

❑ Emulsifying agents

Emulsions are a special **kind of colloidal dispersion in which, one liquid is dispersed in a continuous liquid phase of other liquid.** The **dispersed phase is the internal phase and the continuous phase is external phase.** The system is **stabilized by another substance called emulsifying agent.**

Classification of emulsifying agents

1. Natural:

(a) Vegetable source: Gum acacia, tragacanth, agar, starch, pectin, iris moss

(b) Animal source: wool fat, egg yolk, gelatin.

2. Semi synthetic: Methyl cellulose, Na CMC

3. Synthetic:

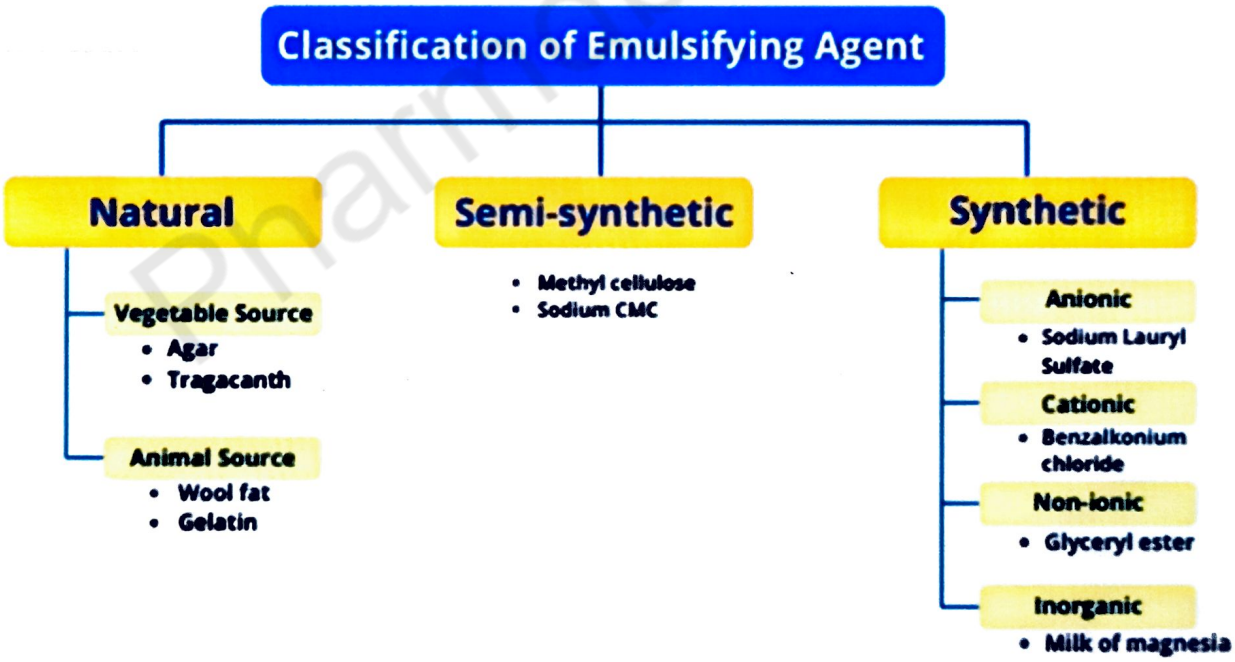
(a) Anionic: Sodium Lauryl Sulphate

(b) Cationic Cetrimide, benzalkonium chloride

(c) Non-ionic: Glyceryl ester-glyceryl monoesters etc.

4. Inorganic: Milk of magnesia, Mg oxide, Mg trioxide etc.

5. Alcohols (polyoles): Carbowax, cholesterol and lecithin.



❑ Semi solid excipients

- Semi-solid dosage forms may be **topical or sterile products when applied to the skin or body cavities that treats the pathological condition and protects it from other harmful environment**. These are a smooth, non-staining dosage forms that get miscible with skin secretions.
- The examples of these dosage forms include **creams, gels, pastes, etc**. While developing semi-solid dosage forms special attention is needed to eliminate any possible interaction between selected excipient with the drug and its environment. Excipients used in **semi-solid dosage forms contribute to about 90% of its total quantity and hence, is important to select right excipient with required functionality.**
- In the development of semi-solid dosage forms, it is crucial to **identify the critical properties of excipients and understand how their variation affects the final quality of drug product**. The source of an excipient typically plays a key role in its inherent variability.

Excipients in semisolid dosage forms

Ointment	Paste	Cream	Gel
Ointment base	Paste base	Penetration enhancer	Gelling agent
Preservatives	Preservatives	Oil/oleaginous substances	Preservative
Anti-oxidant	Anti-oxidant	Emulgents	Hygroscopic substances
Chelating agent	perfume	Co-emulsifiers	Chelating agents.
Humectant		Emulsion stabilizers	
perfume		Mixed emulsifier systems	
		Humectants	
		Stabilizers	
		perfumes	

(a) Structure-forming excipients:

- Semi-solid dosage forms possess **3D structure** which is responsible for their **rheological plastic nature that retains their shape on application of external force.**

(b) Gelling agents:

- Gelling agents are the gel-forming excipients which when dissolve in a **liquid phase as a colloidal mixture forms a weakly cohesive internal structure.**
- They are organic hydrocolloids or hydrophilic inorganic substances such as **tragacanth, pectin, starch, carbomer, sodium alginate, gelatin, cellulose derivatives, polyvinyl alcohol clays, etc.**

(c) Emollients:

- Emollients are excipients that provide **softness and smoothness to the skin and adjust the consistency of semisolids.**
- Ideally emollients must be **non-irritating, non- toxic and mild,** as they may interfere with several skin reactions that may occur after skin damage.

(d) Bases:

- Bases are the vehicle for the drugs used in **semi-solids intended for external use.** Right selection of base for such semisolids depends upon type of activity required, for **example, topical or percutaneous absorption: physicochemical and microbial stability of product; compatibility with other components of the formulation; ease of manufacture; pourability and spread ability of the formulation; duration of contact; risk of hypersensitivity reactions; and ease of washing/removal from the site where applied.**

(i) Hydrocarbon bases:

- Hydrocarbon bases, also known as oleaginous bases, are made up of oleaginous materials.
- They exert an emollient and protective effect upon application to the skin and remain on the skin for a prolonged period of time without drying.

(ii) Absorption bases:

- Absorption bases consist of both water and oil; wherein water is used in small amount as internal phase and oil in high amount as external phase.
- There are two types of absorption bases. First, those that permits the incorporation of aqueous solutions, which results in the formation of w/o emulsions; and second, those that permit incorporation of aqueous solutions in a small amount as they are already w/o emulsions.

(iii) Water-removable bases:

- Water-removable bases are o/w type emulsions containing an emulsifier, which makes them readily miscible with water.
- Due to high water content, they are hydrophilic in nature. Incorporation of a large proportion of aqueous solutions into these bases is possible with the aid of emulsifying agents.

(iv) Water-soluble bases:

- Water-soluble bases contain only the aqueous phase and thus, they are hydrophilic in nature.
- The water-soluble bases have the advantages of being water soluble and washable, Non-greasy, non-staining, non/less occlusive, lipid free, relatively inert and does not support mold growth.
- They undergo little hydrolysis and are stable but may dehydrate skin and hinder percutaneous absorption.

(v) Miscellaneous bases:

- Miscellaneous bases include the mixture of hydrocarbons and water-soluble bases. Some bases from this category are w/o emulsions capable of dispersing in the aqueous solutions.