UNIT-3

Advanced study of Pharmaceutical Excipients-II

Points to be covered in this topic

- Pharmaceutical Excipients in pharmaceutical product development
- Tablet and capsule excipient
- Directly compressible vehicles
- Coat material
- Excipients in parenteral and aerosols products
- Excipients for formulation of NDDS

❑ Pharmaceutical Excipients in pharmaceutical product development with a special reference to the following categories

- Excipients are essential parts of a formulation that make it possible for the medications to be **delivered, manufactured, and stable.**
- New excipients are required to support the **delivery, production, and development** of such drug products as new medications become more difficult to synthesize.
- A number of innovative excipients have recently been successfully used in the **manufacture of medicinal products**. To **improve the production** process for drugs in conventional dosage forms and to improve stability for a longer product shelf life, new excipients are being developed.
- These new excipients present potential as well as obstacles that could be significant. Using them in **solid dosage forms presents a number of challenges, such as the need for solubilizers to address drug delivery issues with poorly water-soluble medications, the need for the ideal filler-binder for direct compression tablet manufacturing, the increased speed of tablet machines and manufacturing efficiency driving the demand for excipients with good compressibility and low weight variation at shorter dwell times, and the need to address loss of compaction with wet granulation and high moisture content.**
- In order to **increase the quality and safety** of the medication or **lower its production costs**, approved medications may be reformulated with the assistance of new excipients. These excipients should possess **ideal pharmacokinetic characteristics.**

❑ Tablet and capsule excipient

- Excipients are used to help **formulate suitable tablets and capsules, to aid in overall manufacturing process, to enhance drug delivery and thus, contribute to overall acceptance by the patient.**
- Many different excipients are used in the formulation of tablets and capsules. Properties of these excipients in pharmaceutical formulation plays major role in determining the **stability and effectiveness**.
- Excipients used in tablet and capsule manufacturing acts as **binders, diluents, lubricants, disintegrating agents, plasticizers, solvents, cosolvents, buffers, antimicrobial agents, emulsifying agents, sweetening agents, flavors, etc.**
- Ideally excipients are inert but some excipients offer **therapeutic properties** as well, for example, guar gum (laxative), sucrose (nutrient), chloroform (anesthetic), aromatic waters (carminative), etc.
- Certain artificial excipients used as binders, fillers and flow enhancing agents are **hazardous to human health**.
- These are added to produce a custom **color to a formulation or fillers to increase bulk in tablets and capsules, as flow enhancing agents to allow mixing of various ingredients, and as lubricants to ease filling of capsules and movement of powder during processing.**

The common ideal properties of excipients for a tablet and capsule dosage form are as follows:

(a) They must be physico-chemically and therapeutically inert, non-toxic and compatible.

(b) Odourless, tasteless, elegant and pharmaceutically acceptable.

(c) Biologically stable, could be standardized, tested and delivered and approved by regulatory bodies.

(d) Easily available, economic, highly flexible, sterilizable and physico-chemically and 24s biologically stable.

(a) Binders:

- Most of the drugs added to the tablet formulations are in such an amount that renders them unsuitable for compaction.
- Excipients may be added to enhance this property through their **small size and intermolecular attraction to decrease the volume** occupied.
- Binder **decreases surface area, increases cohesiveness, and improve flow** properties of the powdered raw materials.
- These are used to give a definite shape and size to the powder ingredients to get a product having the **required flow properties.**

The binders may be classified as:

S.No.	Class	Binders
01	Natural source	Gum acacia (10-20%), gum tragacanthins (10-15%), etc.
02	Animal source	Chitin, chitosan, etc.
03	Microbial source	Xanthan, dextran, etc.
04	Marine source	Agar, alginic acid, etc
05	Semisynthetic and synthetic gums and polymers	Carboxymethylcellulose, hydroxypropyl methylcellulose (2-10%), polyvinyl pyrrolidone, etc.
06	Sugars and cellulose derivatives	Starch paste (5-10%), glucose, polyethylene berts glycols, sorbitol (10-25%), etc.
07	Inorganic minerals	Bentonite (up to 25%), tribasic calcium phosphate (10-30%), calcium carbonate (>50%), etc.
08	Solvents	Isopropyl alcohols, ethanol, polyvinyl alcohol (5-20%), etc.

(b) Antiadherants and lubricants:

- Antiadherants and lubricants **decrease the friction at the die wall** by forming a film of low to **very low shear strength at the interface** between the **die cavity or mold and the mass** that has been added to it.
- This causes **decrease in sticking and adherence** to the machines and help in the release from the equipment with no or minimal friction and breakage.
- The lubricants may be **water soluble or water insoluble in nature.**
- Stearic acid is used but is less effective than magnesium stearate and mostly used along with it. In combination, **talc, glyceryl behenate, and sodium stearate fumarates are also used as lubricants.**

(c) Glidants:

- Glidants enhance the flow characteristics of a powder mixture. To get the **desired effect, these are added as a dry powder before the compression process.**
- Glidants acts by **decreasing the overall surface charge** present on the surface of powder blend, **decreasing friction between particles of the blend and filling in the gaps on the surface, enhancing the rate of movement and flow.**

(d) Sorbents:

- Sorbents are substances that have property to **adsorb liquids or gases.**
- These may act as a molecular sieve attracting the substance on their surfaces.

(e) Disintegrants:

- Disintegrants help the tablet to **break into its components as granules or fine powder.**
- These excipients are used alone or in combination with others to

- facilitate dispersion and breakup of tablets/granules in capsules into their basic components for faster dissolution upon contact with the **dissolution medium**.
- The natural disintegrants includes **starches and celluloses, gums, alginates, inorganic clays, enzymes (cellulases, diastases), bentonite, kaolin and swelling agents. Synthetic disintegrants are surfactants, starch derivatives and various polymers.**

(f) Diluents:

- Diluents, also known as **bulk additives**, are inert powders acting as fillers in the tablets and capsules.
- These are added to **increase the weight** of the final formulation and enhance cohesion, flow properties, and shape of the dosage form.
- Diluents are selected on the basis of **inertness, economy and cost, organoleptic properties, moisture content and uptake, compactness, compatibility with drug and other additives, binding ability, hardness** and friability, swelling properties, disintegration behavior, resistance toward microbial growth and stability.

(g) Flavoring agents:

- Flavoring agents are **organoleptic agents** used to enhance elegance and aesthetic appearance of the formulations.
- These are added to **increase patient compliance through masking unpleasant taste, complementing color and sweeteners** used and help in product identification.
- The **examples** of flavoring agents used in tablets and capsules include bitter flavors (anise, mint, or chocolate), sour flavors (berries, orange, lemon), sweet flavor (fruits, sugars) and salty flavor (butterscotch, vanilla, peach).

(h) Sweeteners:

- Sweeteners are added to **mask the taste of salty and bitter drugs** and/or excipients in tablets and capsules.
- They significantly improve patient compliance.
- **Sucrose** is the most common **low-cost sweetener** available in different shapes and sizes as powder, small or large granules, etc.
- It is **not suitable for health conscious and diabetic patients**.

(i) Coloring agent:

- Colors are added in association with the flavors to complement their effect and also **to increase product elegance.**
- They are used to **mask poor color of the drug and other additives, enhance appeal and for the product identity.**

(i) Preservatives:

- The preservatives are added to prolong the shelf life of the formulation and to maintain the sterility of the formulation by **preventing the growth of micro-organisms for a proposed shelf life.**
- Based upon mechanism of action preservatives are categorized as **antioxidants, antimicrobial agents and chelating agents.**

❑ Directly compressible vehicles

- The preferred method for creating tablets is direct compression.
- Directly compressible vehicles or direct compression fillers and binders are other names for direct compression excipients.
- These substances are **pharmacologically inert and can be compressed easily, even when combined with medications.**
- The **flowability and compressibility of powder mixtures are improved by these vehicles during the direct compression method of making tablets.**

➢ Properties:

An ideal direct compressible vehicle should preferably have the following properties:

1. The materials should have high flowability to enable uniform fill of the dies.
2. It should have sufficient cohesive properties to form a firm, strong tablet under adequate compressional force.
3. They should be physiologically safe and should not interfere with the bioavailability Jag of drugs.
4. They should be stable and compatible with all types of drugs and packaging material(s).
5. High dilution potential and capable of reprocessing without loss of flow/compressibility.
6. Colourless, tasteless and should accept colorants uniformly.
7. Cheaply available and possess proper mouth feel.
8. They should not allow microbiological growth.
9. They should have particle size equivalent to drugs.
10. Possess good pressure-hardness profile and blend should have an optimum bulk density.

➢ Methods of Preparation

(a) Chemical modification: Chemical modification method is relatively **expensive and time consuming** for preparing directly compressible vehicles. Chemical modification is carried out by alteration of **excipient properties by cross-linking or through substitution, condensation, hydrolysis reactions of the parent excipient or new chemical species.**

(b) Physical modification: Physical modification is **simple and economical method** that involves varying and optimizing the physical properties of excipients for specific application. Examples of physically **modified directly compressible vehicles are dextrates and sorbitol.**

(c) Grinding and/or sieving: This method involves **grinding and/or sieving of materials to produce excipients having controlled size and flow properties.**

(d) Crystallization: Crystallization is the **process of forming crystalline solids**. Controlled crystallization from aqueous solution produces crystalline solid excipients that impart flowability to the powder blend.

(e) Spray drying: Spray drying is extensively used to **prepare uniform size, free flowing direct compressible excipients**. The spherical shape and uniform size of these materials exhibits **good flowability but has poor reprocess ability.**

(f) Granulation: Granulation involves the addition of an **aqueous dispersion of granulating agent to a mixture of excipient blend**, followed by drying and sieving. The product of granulation is **irregular in shape and size.**

➢ Classification

According to Wells and Langridge, direct compressible vehicles may be classified based on their disintegration and flow properties as follows:

(1) Disintegration agents with poor flow: MCC (Avicel), microfine cellulose (Elcema), directly compressible starch (StaRx 1500), etc.

(2) Free flowing materials which do not disintegrate: Dibasic calcium phosphate (Emcompress).

(3) Free flowing powders which disintegrate by dissolution: Spray dried lactose anhydrous lactose, spray-crystallized maltose-dextrose (Emdex), sucrose, dextrose, amylose, mannitol, etc.

(4) Optimum tableting compression characteristics: Blends of materials with disintegrant properties (1 and 3) and free flow properties (2 and 3).

❑ Coat material

- A coating is a covering that is put on an object's surface, also known as the substrate. Excipients are frequently **coated on tablets, pellets, granules, capsules, powders, and crystals.**
- The complicated coating process creates a thin layer around the particles. This layer typically ranges in thickness from **20 to 200 m** and represents **1 to 9% of the initial solid weight.**
- The formulation of the film coating is essential for solid oral dosage forms. Excipients for coating that are highly functional and provide a film coating are used for various purposes. Conventional coatings help to **conceal unpleasant tastes, identify products, make things easier to swallow, improve stability, and/or improve handling** characteristics. Drug release from the dosage form is altered by functional coatings.
- Some pharmaceutical companies develop and manufacture their own coating products, but many others instead purchase fully formulated materials to save on costs and improve efficiency and product consistency.

The composition of a typical coating formula includes:

1. **Polymers:** Polymer is a **backbone of the coating layer**. Examples: Cellulosics (HPMC, HPC and EC), vinyls (PVA), acrylics for enteric or delayed release coatings (methacrylic acid and ethylacrylate copolymers) and natural derivatives (shellac or alginates).

2. **Plasticizing agent:** Plasticizers are relatively low molecular weight materials which have **capacity to alter the physical properties of a polymer** to render it more useful in performing its function as a film coating material. They **reduce the film forming temperature of the polymer** and make it possible to apply at lower temperatures, and improve the elasticity of the coating film.

3. Colorants and pigments: These excipients are used to **increase opacity, light protection and provide coloration**. **Examples:** Water insoluble lakes (indigo carmine, tartrazine, allura red, and quinoline yellow) and water soluble dyes of these same colors, inorganic pigments (titanium dioxide, iron oxides) and pearlescent pigments containing mica and natural colorants (vegetable juice, carotenoids and turmeric).

4. Glidants: Glidants are incorporated to produce **smooth and tack-free coats.** **Examples:** Talc, carnauba wax, inorganic stearates, etc.

5. Flavors: Flavors are used to **improve the patient compliance and to create brand value**. Examples: Natural or artificial flavors (mint, vanilla, berry, etc.)

6. Sweeteners: These are **natural or high intensity artificial substances for taste**. Examples: Sucralose, NEOSORB (sorbitol solution), LYCASIN (liquid maltitol), etc.

7. Viscosity modifiers: These materials allow coatings to be applied **more efficiently to create an improved tablet appearance**. **Examples:** Carbohydrates (lactose, polydextrose, or starch) and gums (acacia or xanthan gum).

❑ Excipients in parenteral

- Parenteral preparations are sterile preparations intended for administration by **injection, infusion, or implantation** into the human or animal body.

- These products must be **sterile, pyrogen-free**, and, in the case of solution, free of particulate matter.
- It needs **no flavoring and sweetening agents** for its palatability.
- The products should preferably be **isotonic, and depending on the route of administration,** there are some constraints on use of certain excipients. Usually for parenteral products, ultra high purity grades of excipients are used.
- Those excipients which withstand at terminal sterilization or aseptic processing are preferentially selected. **FDA** approved safe excipients that **increases the assurance of product quality is safe** to be used. Using them in combination with other excipients does not give complete assurance as this may lead to unwanted potentiation or synergistic toxic effects.

Criteria for the Selection of Excipients

The following key points are considered in selecting an excipient for parenteral products:

(1) Excipient's influence on the overall quality of drug product.

(2) Their compatibility with drug, the packaging system and with the manufacturing process.

(3) Amount of excipients to be added to the drug product.

(4) Route of administration.

(5) Dose and product volume

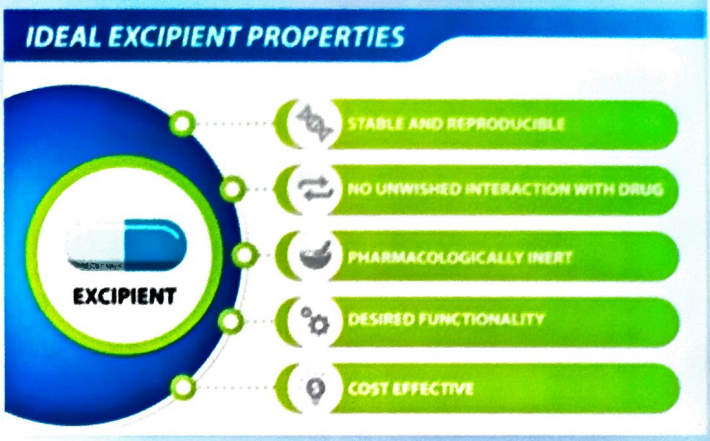
(6) Type of use (single dose or multiple dose).

(7) Length of time over the drug product used upon opening multidose product.

➤ EXCIPIENTS USED IN LIQUID PARENTERAL:

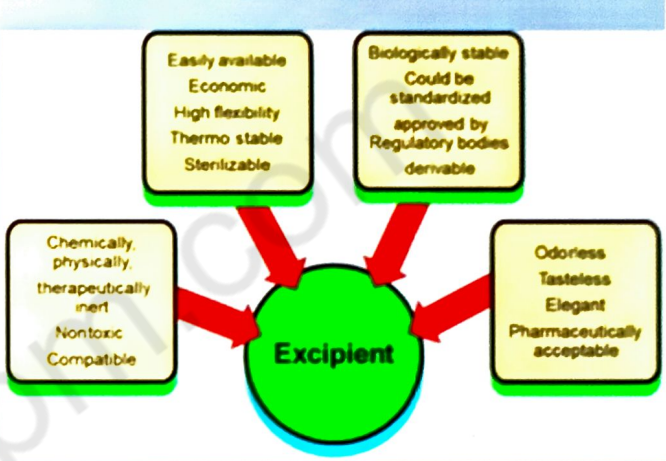
❖ For solution parenterals

- Tonicity adjusting agents
- Preservatives
- Solubilizing agents
- Complexing agents
- Buffering agents
- Antioxidants



❖ For emulsion parenterals

- Oils
- Emulsifiers
- Aqueous phase
- Preservatives



❖ For suspension parenterals

- Flocculating agents
- Wetting agents
- Solvents
- Preservatives

❖ For solution parenterals

(a) Tonicity adjusting agents

Parenteral formulations should be isotonic with body fluids to avoid damage to the cells and tissues. **Usually drugs are not isotonic with body fluids and thus, require addition of a tonicity adjusting agents to the formulation.**

(b) Preservatives

Multidose liquid parenteral products need preservatives that function as antioxidants, antimicrobial and chelating agents.

(c) Solubilizing agents

Solubilizing agents help to **dissolve or increase the solubility of drug into the formulation.** The **surfactants increase the dissolution by reducing the surface tension of the drug substances whereas, co-solvents imparts hydro- or lipophilicity to drugs in conjunction with another solvent to dissolve a solute.**

(d) Complexing agents

Many drugs are poorly soluble with in water. Complexing agents (co-solvents) are used to **enhance the aqueous solubility of such drugs.**

(e) Buffering agents

Buffers are added to parenteral formulation to **adjust pH range of buffer capacity and maintain pKa, optimize drug solubility and stability.**

(f) Antioxidants

Some **small drug molecules are susceptible to oxidation which can affect the drug product quality.** Reducing oxygen is often accomplished by flushing or sparging with nitrogen or argon.

❖ For Emulsion Parentrals:

- Parenteral emulsions are **best source of calories and essential fatty acids.**
- Their **physical properties and low toxicity** make them excellent vehicles for the formulation and delivery of drugs with a broad range of applications. These applications include **enhanced solubilization or stabilization of the contained drug to sustained release and site-specific delivery.**
- They are composed of **oil phase, aqueous phase and emulsifiers, pH adjusting substances, etc.**

(a) Oils

Long-chain triglycerides (LCTs) or medium-chain triglycerides (MCTs) are most safflower oil, whereas MCTs are obtained by the re-esterification of fractionated coconut oil fatty acids (mainly caprylic and capric) with glycerin. These oils have long-term commercial acceptability in parenteral emulsions, and are found in several FDA-approved products.

(b) Emulsifiers

Natural and synthetic agents are most often used because oils do not form a spontaneous emulsion when mixed with water. The most commonly used **emulsifier is natural lecithin.**

(c) Aqueous phase

The aqueous phase may contain **ionic or osmotic agents, antioxidants, buffers and preservatives, in addition to water.** Because emulsified oil exerts no osmotic effect, isotonic adjustment (to 280-300 mOsm/kg) is important for large-volume parenterals, for example, injectable fat emulsions.

(d) Preservatives

All **small-volume parenteral emulsions should include an antimicrobial agent because the aqueous, external phase is most vulnerable to inadvertent contamination.** These agents can be dissolved in the aqueous phase prior to emulsification.

❖ For Suspension Parenterals:

Parenterally insoluble or poorly soluble drugs are administered as suspension. The particle size of drug is very fine with large surface area that **helps to ensure a high degree bioavailability.**

(a) Flocculating agents

During storage, **suspensions may aggregate to form compact mass at the bottom of container losing its homogenous character**. Therefore, flocculating (suspending) agents are added to **form loosely bound flocs that settles rapidly are redisperse easily upon shaking.**

(b) Wetting Agents

Wetting agents are used to **reduce the contact angle between the surface of the drug particle and the wetting liquid to obtain maximum wetting efficiency.** They **enhance resuspendability and impart viscosity**. Usually, surfactants with HLB value 7-9 are selected.

(c) Solvents

Aqueous or non-aqueous vehicles are used as solvent systems in parenteral suspension. Choice depends on solubility, stability and desired release characteristics of the dispersed drug. Water for Injection is preferred solvent of choice in most parenteral suspensions.

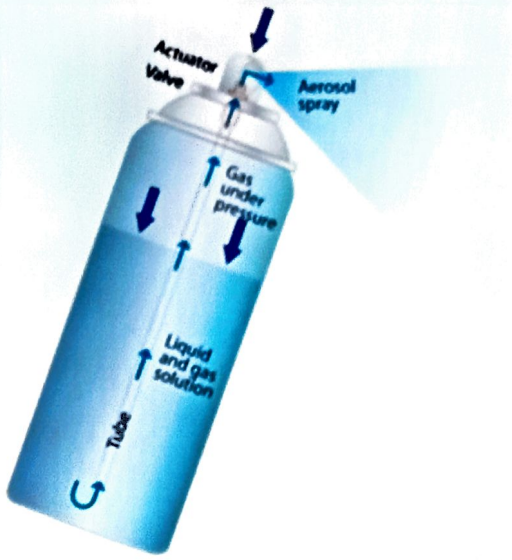
(d) Preservatives

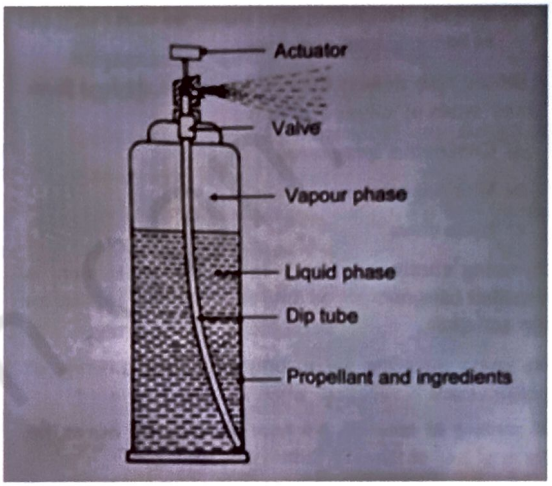
Antimicrobial agents are added in multiple dosing **parenteral products to protect the product from accidental microbial contamination during use at the time of administration. Commonly used preservatives with their concentrations are benzyl alcohol (0.9% to 1.5%), methyl paraben (0.18% to 0.2%), propyl paraben (0.02%), thiomersal (0.001% to 0.01%), etc.**

❑ Excipients in Aerosols Products

- Pharmaceutical aerosol consists of extremely fine **solid or liquid particles** that remain suspended in a gas or air, called propellant.
- These aerosols are fine particles of **drug packaged in a container under pressure that release contents as fine spray when a button is pressed.**

- Aerosols can have variations in formulation depending upon site of application and desired use.
- There are two types of inhalers called **Metered-Dose Inhalers (MDIs) and Dry Powder Inhalers (DPIs)**. Both deliver a specific dose of drug internally to the lungs through pulmonary tracks and topically on surface of body parts.
- Aerosol formulations are NDDS that deliver drugs to the systemic circulation for faster local action. Recently, new excipients are being used to achieve better formulation efficacy and patient compliance.





(1) Propellants:

- Propellants are important components of pressurized MDIs that perform the **function of expelling the product from the container** by supplying the necessary pressure **within the aerosol system.**
- They are liquefied or compounded **gases having higher vapour pressures** employed to obtain the necessary delivery and spray characteristics of the aerosol.
- The commonly used propellants in aerosol systems are hydrocarbons, especially the **fluorochloro** derivatives of methane and ethane, the butanes, pentanes and compressed gas.
- **The basic characteristics of any propellant are**

(a) Chlorofluorocarbons (CFCs)

(b) Hydrofluorocarbon (HFC) and hydrochlorofluorocarbon (HCFC)

(c) Hydrocarbons

(d) Compressed gas

(2) Solvents:

Solvents may be added to the aerosol formulation to **retard the evaporation of the propellant.** Solution aerosols can be difficult to formulate because many propellants or propellant-solvent mixtures are non-polar and are poor solvents for the product concentrate. **Solvents are usually liquid, but can also be a solid or a gas.**

(3) Co-solvents

Often co-solvents are employed in aerosol formulations to **increase the solubility of poor water soluble substances and/or to enhance the chemical stability of drugs.** The polar co-solvents help to enhance solubility, mask taste as well as smell and as an antimicrobial agent.

(4) Buffering agents

Buffering agents help to **maintain the acidity of an aerosol formulation in solution form.** The maintenance of desired pH of the formulation is necessary to ensure physiological compatibility, maintain stability of the drugs and excipients and for the antimicrobial effectiveness as well as solubility of formulation components. Commonly used buffering agents include **sodium bicarbonate, magnesium carbonate and sodium citrate, etc.**

(5) Preservatives

Preservatives prevent an **increased risk of contamination and proliferation by opportunistic microbes.** Ideal properties of these types of excipients are mostly targeted to microbial cells and have no toxicity towards mammalian cells.

(6) Antioxidants

Antioxidant substances are added to **prevent or delay formulation deterioration from the action of air.** For **example, some preservative (potassium sorbate) cause oxidation of drugs, some vehicles (oils or fats) are prone to rancidification and some colorants undergo**

(7) Surfactants

Surfactants used in **emulsion aerosols have included fatty acids saponified with triethanolamine, anionic surfactants**, and more recently **non-ionic surfactants** such as the **polyoxyethylene fatty esters, polyoxyethylene sorbitan esters, alkyl phenoxyethanols, and alkanolamides**.

(8) Wetting agents

Wetting agents are used in **liquid aerosols to reduce surface tension and make it more effective in spreading over and penetrating surfaces**. They are also used as **suspending agents to encourage deflocculation at low level.** The **examples of wetting agents include Tweens, Spans, poloxamers, lecithin, SLS, etc.**

(9) Anti-foaming agents (Defoamer)

Antifoaming agent (defoamer) is used to **reduce foam formation in liquid dosage formulation.** Foaming is encountered during processing or at reconstitution. Antifoaming agents are **effective in reducing foams by lowering surface tension and cohesive binding of the liquid phase**.

(11) Biodegradable polymers

Biodegradable polymeric microspheres are used as **sustained release pulmonary drug carriers**. For **example, polylactic acid and poly glycolic acid are used to achieve sustained-release profiles of drugs, for example,, corticosteroids.**

(12) Liposomes

Liposomes are vesicles prepared from **phospholipids with or without cholesterol and structurally have one or more lipid bilayers, separated by aqueous compartments, surrounding an aqueous core.**

(13) Large porous particles

Pulmosphere is the new type of aerosol formulation that comprises of large porous hollow particles. They have **low particle densities, excellent dispersibility and can be used in both MDI and DPI systems.** These particles can be prepared with polymeric or non-polymeric excipients, using solvent evaporation and spray-drying techniques.

(14) Polymeric nanoparticulate system

The polymeric nanoparticulate system (PNS) is used to **carry the drug molecules to protect them from degradation, and to control its release.**

(15) Solid lipid nanoparticles:

Solid lipid nanoparticles (SLNs) are made from solid lipids, surfactant(s) and water. It has been used as **an alternative to polymeric nanoparticles.** They provide **drug release from SLNs in the lung in a control manner achieving prolonged release and faster in vivo degradation.**

❑ Excipients for formulation of NDDS

- In the order to eliminate limitation of current dosage form; new strategies such as **controlling the pharmacokinetics, pharmacodynamics, non-specific toxicity, immunogenicity, biorecognition, and efficacy of drugs** are employed that improves therapeutic efficacy of drug products called as New Drug Delivery Systems (NDDS).
- These NDDS are based on interdisciplinary approaches that combine **polymer science, pharmaceutics, bioconjugate chemistry, and molecular biology.**
- Various goals those can be accomplished employing NDDS include prevention of drug degradation and loss, reduction in harmful

side-effects and increase in required fraction of the drug at the site of action and increase in drug bioavailability.

- These carriers **soluble polymers, polymeric microparticles, microcapsules, cells and cell ghosts, lipoproteins, liposomes and micelles.**

(a) Nanoparticles:

- Nanoparticles (nanospheres and nano capsules) are either **amorphous or crystalline** forms that adsorb and/or encapsulate a drug and thus, protect it against chemical and enzymatic degradation.
- Nanocapsules are vesicular systems, while nanospheres are matrix systems.
- Nanoparticles as a drug carrier can be formed from both **biodegradable polymers and non-biodegradable polymers..**

(b) Micelles:

- Micelles are **3-50 nm size** self-associated assemblies of amphiphilic block copolymers in aqueous solutions.
- These are employed for delivery of **poor water soluble drug**. The drug molecules are physically entrapped in the core of micelles and transported at concentrations that can exceed their intrinsic water-solubility.

(c) Liposomes:

- Liposome consists of **one or more phospholipid bilayers**. The polar character of the liposomal core enables polar drug molecules to be encapsulated.
- **Amphiphilic and lipophilic molecules are solubilized within the phospholipid bilayer based on their affinity to the phospholipids.**

(d) Dendrimers:

- Dendrimers are **nanosized, highly branched monodispersed macromolecules with symmetrical architecture.**
- They consist of a **central core, branching units and terminal functional groups.**

(e) Liquid crystals:

- Liquid crystals have properties of **both liquid and solid states.**
- They can be made to form different geometries, with **alternative polar and non-polar layers, also called lamellar phase, where aqueous drug solutions can be incorporated.**

(f) Controlled drug delivery system (CDDS):

- Drug release from the delivery system can be controlled by using various materials.
- These includes **insoluble plastic materials like PVP and fatty acids (rigid matrix diffusion); hydrophilic gums like guar gum, tragacanth, HPMC, CMC, xanthan gum and polyacrylamides for sustaining/controlling the release of highly water soluble drugs (swelling matrix diffusion) and non-biodegradable polymers such as silicones, poly(urethanes), poly(acrylates); copolymers such as poly(ethyelene vinyl acetate); biodegradable polymers such as poly(caprolactone) (PCL), poly(lactic acid) (PLA), poly(lactic- co-glycolic acid) (reservoir system).**

(g) Colon specific DDS:

- This system is used in **the systemic delivery of enzymes, vaccines, growth hormones, protein and peptide drugs, etc.**
- These drugs are inactivated or destroyed in acidic environment of **stomach and the parenteral route** for their delivery is not convenient and safe.

(h) Pulmonary drug delivery:

Pulmonary drug delivery is the inhalation of drug formulation through **mouth and the further deposition of inhaled drug in lower airways**. Three main inhalation systems for the aerosolization of drugs are nebulizers, pressurized MDIs and DPIs.

(i) Aquasomes:

Aquasomes are like **'bodies of water that help to protect and preserve fragile biologicals.** They are **three layered structures composed of solid phase nanocrystalline core coated with oligomeric film to which drug or biological moieties are adsorbed with or without modification.**

(j) Niosomes:

Niosomes are drug carriers that have a bilayer structure and are formed by **self-association of non-ionic surfactants and cholesterol in an aqueous phase**. They are **biodegradable, biocompatible, and non-immunogenic** and have **long shelf life, exhibit high stability, and enable the delivery of drug at target site in a controlled and/or sustained manner.**

❑ Excipients in pharmaceutical formulations

- Drugs, as they cannot be administrated as such, are modified to prepare various dosage forms in order to achieve patient compliance, dose accuracy and consistency; improve bioavailability and aesthetics; and reduce side effects.
- Sophisticated excipients perform multifunctional roles and thus, have applications in the area of product development such as; **improvement of the stability and bioavailability of the active ingredient, enhancement of patient acceptability and performance of technological functions that ensure ease of manufacture.**

➢ Selection:

- Excipients can have a considerable impact on any formulation.
- An excipient must best suit the intended dosage form of the drug, demonstrate great **organoleptic properties, conform to pharmacopeial regulations, be easy to source, and work effectively**. The right excipient exhibits ideal pharmacokinetic properties for intended pharmaceutical applications.
- It works well with existing equipment or fit into manufacturing plan..
- Therefore, **selection of excipient(s) for a particular application should consider the properties of drugs, process, target formulation and potential impact on the formulation.**
- The selection of right excipients can **reduce manufacturing costs, improve shelf life and stability, and enhance the patient experience.**
- Currently, excipients that can enhance the solubility compounds are of great interest to formulation scientists.
- Excipients that can offer benefits in easy swallowing and palatability of formulation are essential useful aids for formulation scientists.
- A number of excipients with such attributes are used **in pediatric formulations.**
- Most formulators favor specific excipients for particular types of formulation.
- In the selection process, it is important to consider potential interactions with drug substances. Such interactions can result in assay **irregularities and can reduce the bioavailability**

➢ Applications:

(1) Nanotechnology:

- The most advanced nanoparticulate include **liposomes, albumin nanoparticles and nanocrystals.** PEGylation and its alternatives are used to **improve in vivo stability and reduce immunogenicity.**
- Chemical instability of phospholipid-based systems can be overcome by **freeze-drying, for example, camptothecin-loaded PEGylated phospholipid micelles.**

(2) Taste masking:

Taste masking is important in the **development of pediatric formulations and rapidly disintegrating tablets containing bitter drugs**. Preventing dissolution of the drug in the mouth and contacting the taste buds is one of the mechanisms.

(3) Stabilization of biologics:

- Biologics are primarily administered via **parenteral routes of administration.**
- Great variety of excipients has been used to **reduce frequency of administration, achieve high doses and improved manufacturability of biologic formulations maintaining protein activity on scale-up.**
- Major classes of delivery systems used in biologics formulation include microspheres (PLGA-based, chitosan-based), liposomes (PEGylated lipids) and hydrogels (modified dextran and starch-based). Recently, dendrimer-based polymers are used to achieve polydispersity.

(4) Enhanced processing:

The developments in pharmaceutical processes and equipment especially increase in production rates at low cost, lead to the need for new excipients. The newly developed tablet machines require materials with better compressibility because they operate with shorter dwell and contact times.

(5) Patient compliance:

Some excipients used nowadays are unacceptable for the reasons of patient safety and comfort, for **example, lactose intolerance leads to abdominal cramps, diarrhoea, distension and flatulence**. Therefore, properly designed and developed.

(6) Specialized drug delivery systems:

The development of novel or specialized drug delivery systems require the use of **special excipients.** MDI devices require excipients of a particular size grade and development of mucoadhesive preparations necessitated the utilization of new bio-adhesive polymers.

(7) Rapid and controlled drug release:

HPMC is a commonly used **hydrophilic polymer to achieve matrix based controlled release**. However, direct compression of HPMC-based formulations is challenging because HPMC may impart **poor flow properties to the formulation, causing problems during high-speed tablet manufacturing.**

(8) Improved flow properties and compressibility:

Controlled optimal **particle size and particle-size distribution ensures superior flow properties of excipients without the need to add glidants.** The silicified MCC imparts better flow properties to the powder mixtures.

(9) Oral dispersibility:

Excipients in orally dispersible dosage forms are incorporated to contribute for functionalities such as **rapid dispersion in the presence of limited volume of water, pleasant mouth feel, taste masking, and sufficient mechanical strength.** Rapid dispersion can be achieved by formation of highly porous hydrophilic structures that have ability to rapidly absorb water.

(10) Moisture protection:

Moisture sensitivity of drugs is a big challenge in the development of solid dosage forms. Presence of water molecules may influence intermolecular **interactions, affecting free energy, thermodynamic activity, solubility, dissolution rate, stability and bioavailability of the formulation.**