CHAPTER 5: FORMULATION OF SOLID DOSAGE FORM (TABLET & CAPSULES)

INTRODUCTION

LEARNING OBJECTIVES

The objectives of this unit are to:

- Understand the formulation of solid dosage form.
- Understand the characteristic of tablet and capsule and the making process.

LEARNING OUTCOMES

After completing this unit, student should be able to:

- Explain the solid dosage form formulation characteristic
- Explain the process in tablets dosage form formulation.
- Explain the process in capsules dosage form formulation.
- Describe the function of each ingredients used in solid dosage form formulation.

INTRODUCTION

- A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose.
- The excipients can include:
  1. **Diluents.**
  2. **Binders or granulating agents.**
  3. **Glidants (flow aids).**
  4. **Lubricants** to ensure efficient tableting.
  5. **Disintegrants** to promote tablet break-up in the digestive tract.
  6. **Sweeteners** or **flavors** to enhance taste.
  7. **Pigments** to make the tablets visually attractive.
  8. A **polymer coating** is often applied to make the tablet smoother and easier to swallow, to control the release rate of the active ingredient, to make it more resistant to the environment (extending its shelf life), or to enhance the tablet's appearance.

INTRODUCTION

- The compressed tablet is the most popular dosage form in use today. About two-thirds of all prescriptions are dispensed as solid dosage forms, and half of these are compressed tablets.
- A tablet can be formulated to deliver an accurate dosage to a specific site; it is usually taken orally, but can be administered sublingually, buccally, rectally or intravaginally.
- The tablet is just one of the many forms that an oral drug can take such as syrups, elixirs, suspensions, and emulsions.
- Medicinal tablets were originally made in the shape of a disk of whatever color their components determined, but are now made in many shapes and colors to help distinguish different medicines.
- Tablets are often stamped with symbols, letters, and numbers, which enable them to be identified. Sizes of tablets to be swallowed range from a few millimeters to about a centimeter.

INTRODUCTION

- The use of hard shell capsules is a popular drug delivery method.
- In the hard shell capsule delivery method, dry ingredients are encapsulated by filling and closing a two piece protective shell, typically made of:
  1. **Gelatin.**
  2. **Vegetable or Cellulose polymers.**
- The advantages of using this method include:
  1. **Speed & ease of filling.**
  2. **Protection of the API from oxygen and moisture.**
  3. **Control of release.**
- Also, there are many branding options, since capsules come in a variety of colors and shapes with customized logo opportunities. One of the major challenges in formulating capsules is **maintaining a uniform fill weight,** which is **important for accurate dosing**.

INTRODUCTION

- Lactose has been used for years in capsules as a filling/blending aid due to its low hygroscopicity, inert properties, and most importantly, the availability of various grades with controlled particle size and bulk density.
- Kerry offers every grade of lactose, including Anhydrous, Spray Dried, and Crystalline Monohydrate, and offers a wide range of particles sizes within each lactose type.
- This ensures that we will have a match for any desired particle size or bulk density for accurate blending with any type of API.

5.1: THE FORMULA

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THE FORMULA

- In the tablet-pressing process, it is important that all ingredients be:

Fairly dry.

Powdered or granular.

Uniform in particle size.

Freely flowing.

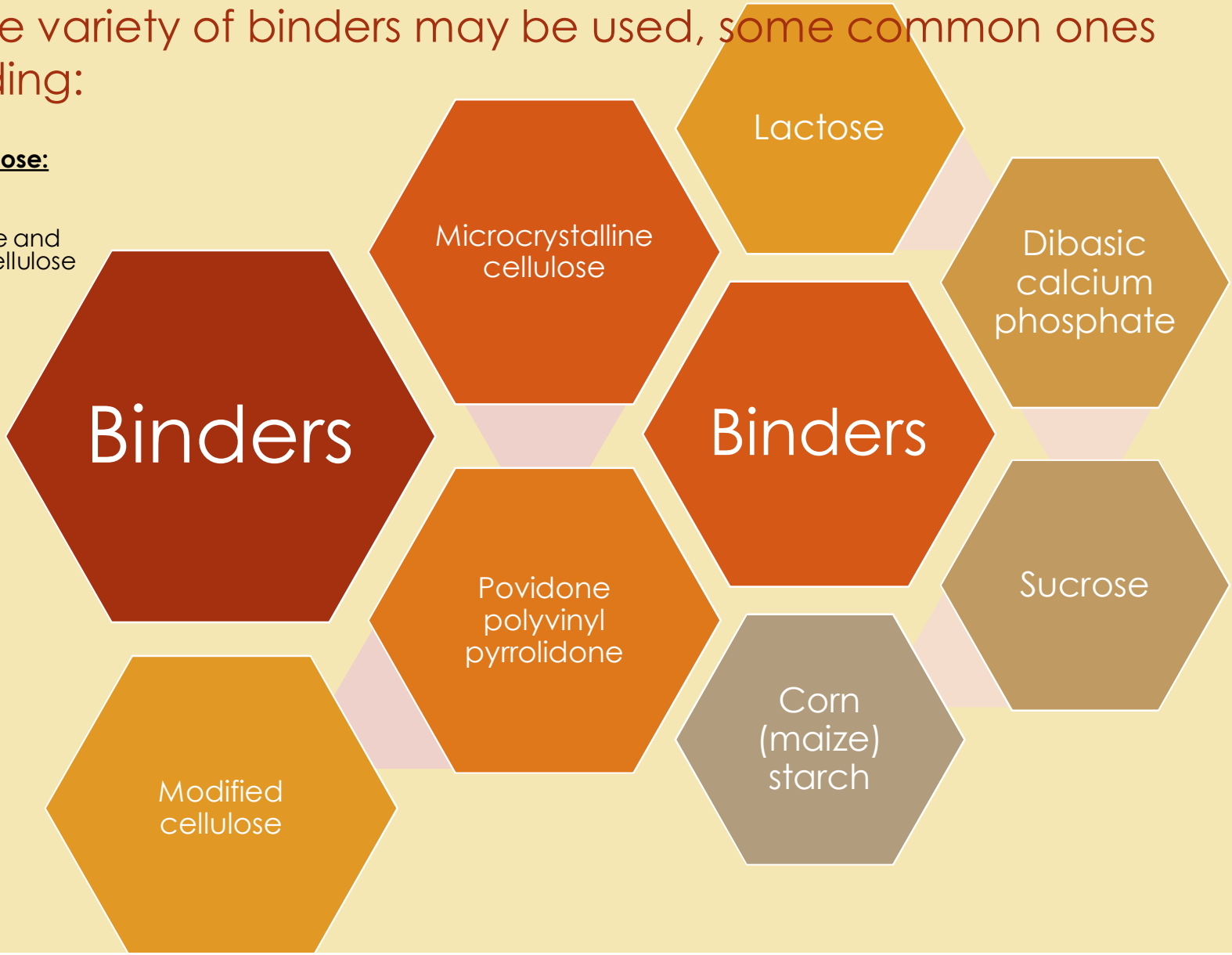
THE FORMULA

- Mixed particle sized powders segregate during manufacturing operations due to different densities, which can result in tablets with poor drug or active pharmaceutical ingredient (API) content uniformity but granulation should prevent this.
- Content uniformity ensures that the same API dose is delivered with each tablet.
- Some APIs may be tableted as pure substances, but this is rarely the case; most formulations include excipients.
- Normally, a pharmacologically inactive ingredient (excipient) termed a **binder** is added to help hold the tablet together and give it strength.

A wide variety of binders may be used, some common ones including:

Modified cellulose:

For example hydroxypropyl methylcellulose and hydroxyethylcellulose



THE FORMULA

- Often, an ingredient is also needed to act as a disintegrant to aid tablet dispersion once swallowed, releasing the API for absorption.
- Some binders, such as starch and cellulose, are also excellent disintegrants.

5.2: THE FUNCTION OF EACH INGREDIENTS

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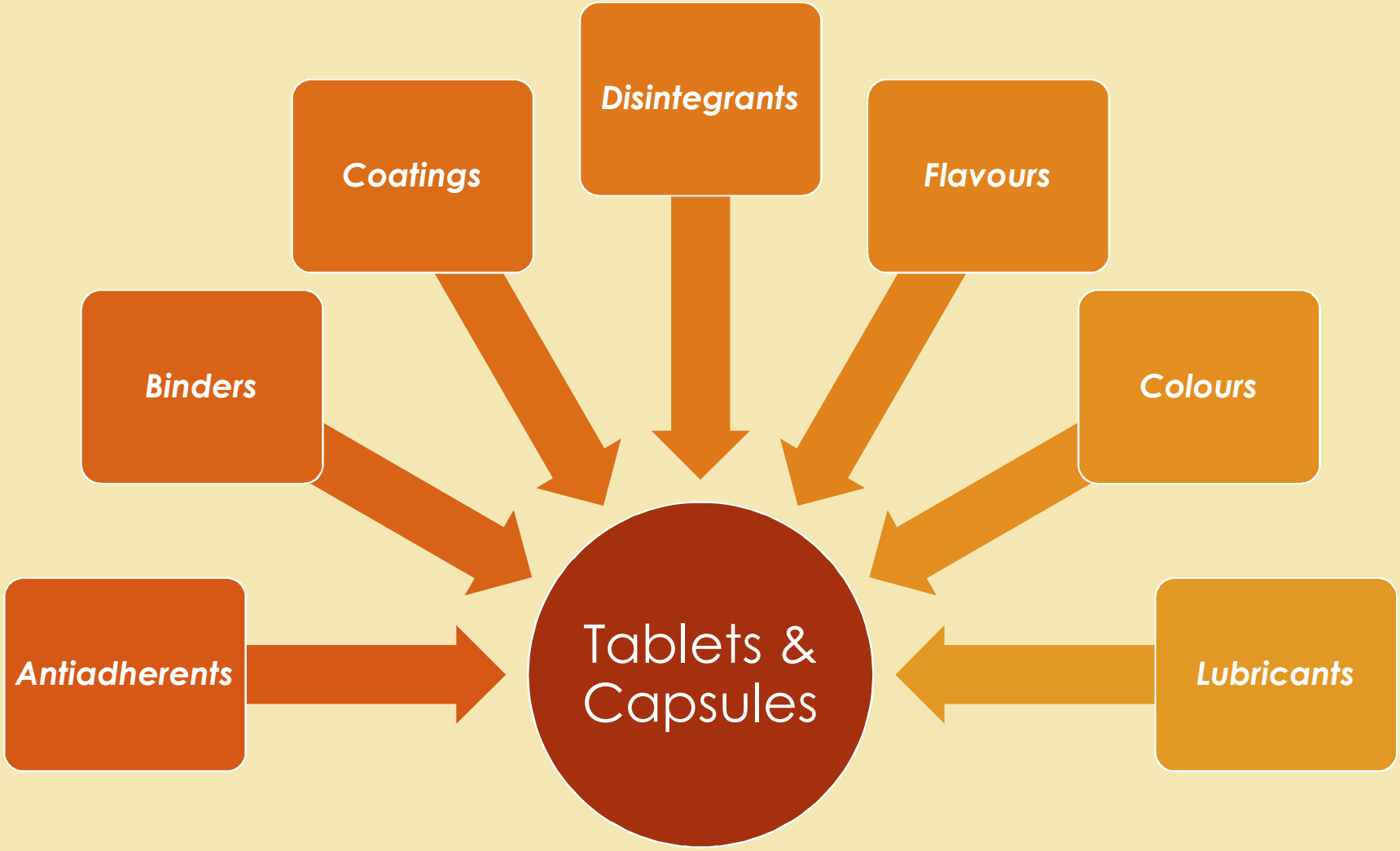
THE FUNCTION OF EACH INGREDIENTS



EXPLANATION

Antiadherents

- Antiadherents are used to reduce the adhesion between the powder (granules) and the punch faces and thus prevent sticking to tablet punches.
- They are also used to help protect tablets from sticking.
- Most commonly used is magnesium stearate.

Talc - **RANGE(%W/W): 1- 5**

Lubricant with excellent antiadherents properties

Cornstarch - **RANGE(%W/W): 3 - 10**

Lubricant with excellent antiadherents properties

Colloidal silica - **RANGE(%W/W): 0.1 – 0.5**

Does not give satisfactory results due to small surface area. Cab-O-Sil and Syloid

DL-Leucine - **RANGE(%W/W): 3 – 10**

Water soluble lubricant; excellent antiadherents properties

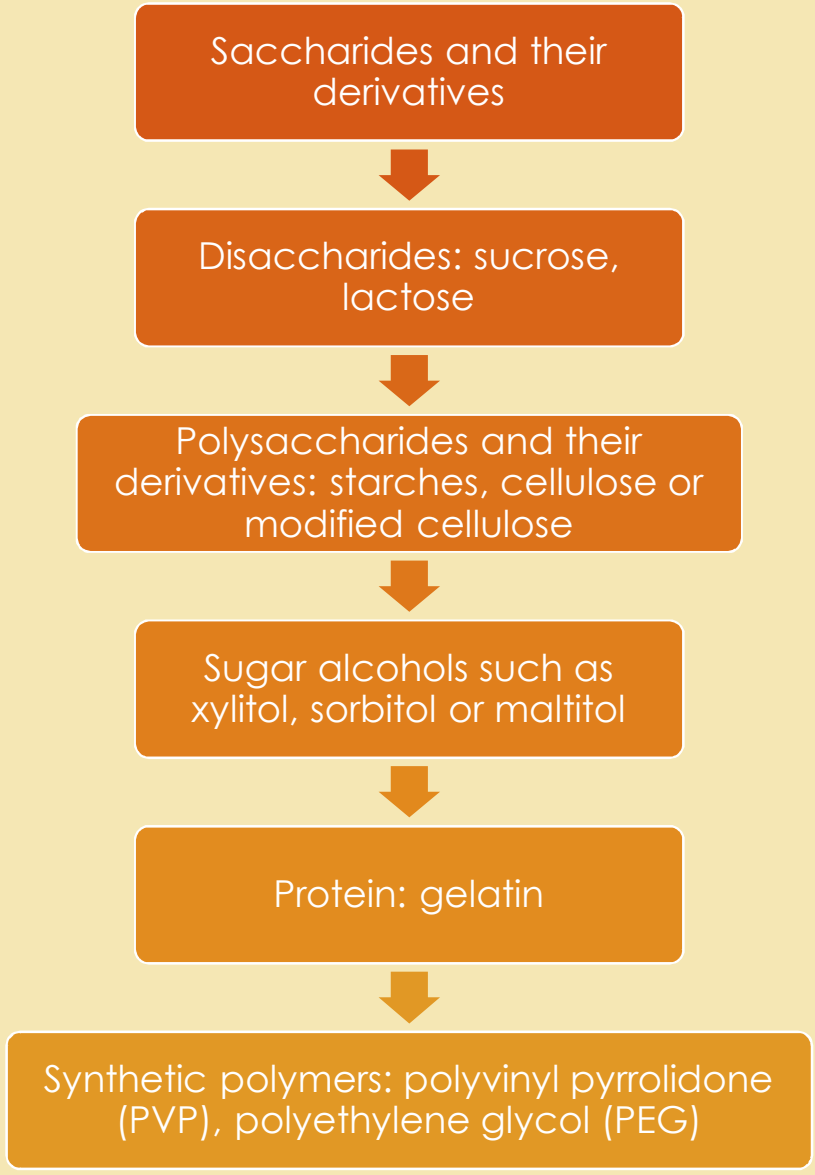
Sodium lauryl sulfate - **RANGE(%W/W): <1**

Antiadherents with water soluble lubricant

EXPLANATION

Binders:

- Binders hold the ingredients in a tablet together.
- Binders ensure that tablets and granules can be formed with required mechanical strength, and give volume to low active dose tablets.
- Binders are usually:>>



Binders are classified according to their application:

Solution binders

- Dissolved in a solvent (for example water or alcohol can be used in wet granulation processes).
- Examples include gelatin, cellulose, cellulose derivatives, polyvinyl pyrrolidone, starch, sucrose and polyethylene glycol.

Dry binders

- Added to the powder blend, either after a wet granulation step, or as part of a direct powder compression (DC) formula.
- Examples include cellulose, methyl cellulose, polyvinylpyrrolidone and polyethylene glycol.

EXPLANATION

Coatings

- Tablet coatings protect tablet ingredients from deterioration by moisture in the air and make large or unpleasant-tasting tablets easier to swallow.
- For most coated tablets, a cellulose ether hydroxypropyl methylcellulose (HPMC) film coating is used which is free of sugar and potential allergens.
- Occasionally, other coating materials are used, for example synthetic polymers, shellac, corn protein zein or other polysaccharides. Capsules are coated with gelatin.
- Enteric control the rate of drug release and determine where the drug will be released in the digestive tract.
- Materials used for enteric coatings include fatty acids, waxes, shellac, plastics, and plant fibers.

EXPLANATION

Disintegrants

- Disintegrants expand and dissolve when wet causing the tablet to break apart in the digestive tract, releasing the active ingredients for absorption.
- They ensure that when the tablet is in contact with water, it rapidly breaks down into smaller fragments, facilitating dissolution.
- Examples of disintegrants include:

Crosslinked polymers: → crosslinked polyvinylpyrrolidone (crospovidone) → crosslinked sodium carboxymethyl cellulose (croscarmellose sodium) → Modified starch sodium starch glycolate.

EXPLANATION

Flavours

- Flavors can be used to mask unpleasant tasting active ingredients and improve the acceptance that the patient will complete a course of medication.
- Flavorings may be natural (e.g. fruit extract) or artificial.

For example, to improve:

- A bitter product - mint, cherry or anise may be used
- A salty product - peach, apricot or liquor ice may be used
- A sour product - raspberry or liquor ice may be used
- An excessively sweet product - vanilla may be used

EXPLANATION

Colors

- Colors are added to improve the appearance of a formulation.
- Color consistency is important as it allows easy identification of a medication.

EXPLANATION

Lubricants

- Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine.
- Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall.
- Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.
- Lubricants are agents added in small quantities to tablet and capsule formulations to improve certain processing characteristics.

There are three roles identified with lubricants as follows:

True lubricant role

- To decrease friction at the interface between a tablet's surface and the die wall during ejection and reduce wear on punches & dies.

Anti-adherent role

- Prevent sticking to punch faces or in the case of encapsulation.
- Prevent sticking to machine dosators, tamping pins, etc.

Glidant role

- Enhance product flow by reducing inter particulate friction.

There are two major types of lubricants:

Hydrophilic

- Generally poor lubricants, no glidant or anti-adherent properties.

Hydrophobic

- Most widely used lubricants in use today are of the hydrophobic category. Hydrophobic lubricants are generally good lubricants and are usually effective at relatively low concentrations.
- Many also have both anti- adherent and glidant properties. For these reasons, hydrophobic lubricants are used much more frequently than hydrophilic compounds. Examples include magnesium stearate.

EXPLANATION

- Lubricants prevent ingredients from clumping together and from sticking to the tablet punches or capsule filling machine.
- Lubricants also ensure that tablet formation and ejection can occur with low friction between the solid and die wall, as well as between granules, which helps in uniform filling of the die.
- Common minerals like talc or silica, and fats, e.g. vegetable stearin, magnesium stearate or stearic acid are the most frequently used lubricants in tablets or hard gelatin capsules.

5.3: TYPE OF EXCIPIENTS

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INTRODUCTION

Definition:

- **An excipient is a natural or synthetic substance formulated alongside the active ingredient of a medication, included for the purpose of bulking-up formulations that contain potent active ingredients (thus often referred to as "bulking agents," "fillers," or "diluents"), or to confer a therapeutic enhancement on the active ingredient in the final dosage form, such as facilitating drug absorption or solubility.**

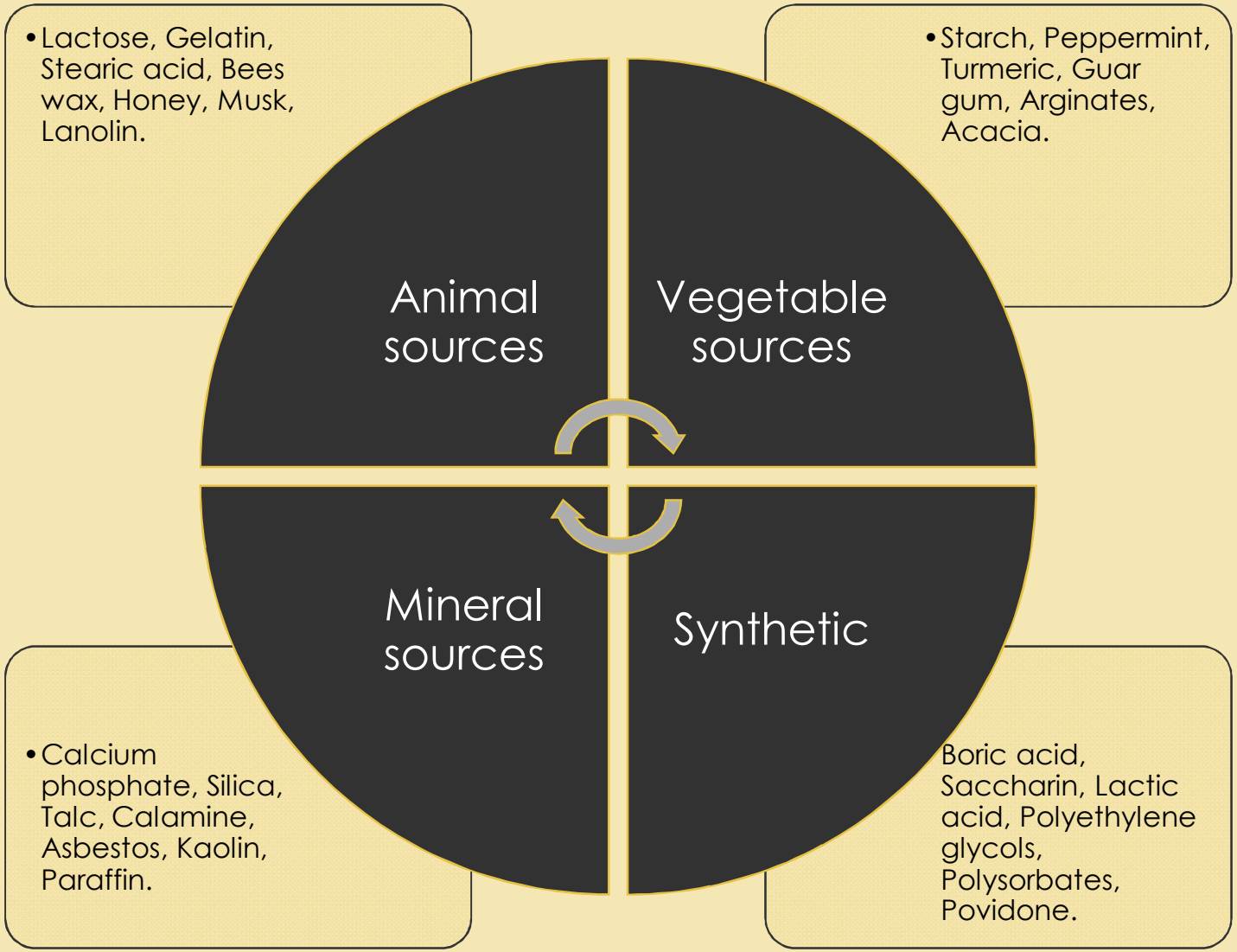
INTRODUCTION

- Excipients can also be useful in the manufacturing process, to aid in the handling of the active substance concerned such as by facilitating powder flow ability or non-stick properties, in addition to aiding in vitro stability such as prevention of denaturation over the expected shelf life.
- The selection of appropriate excipients also depends upon the route of administration and the dosage form, as well as the active ingredient and other factors. Though excipients were at one time considered to be "inactive" ingredients, they are now understood to be "a key determinant of dosage form performance"

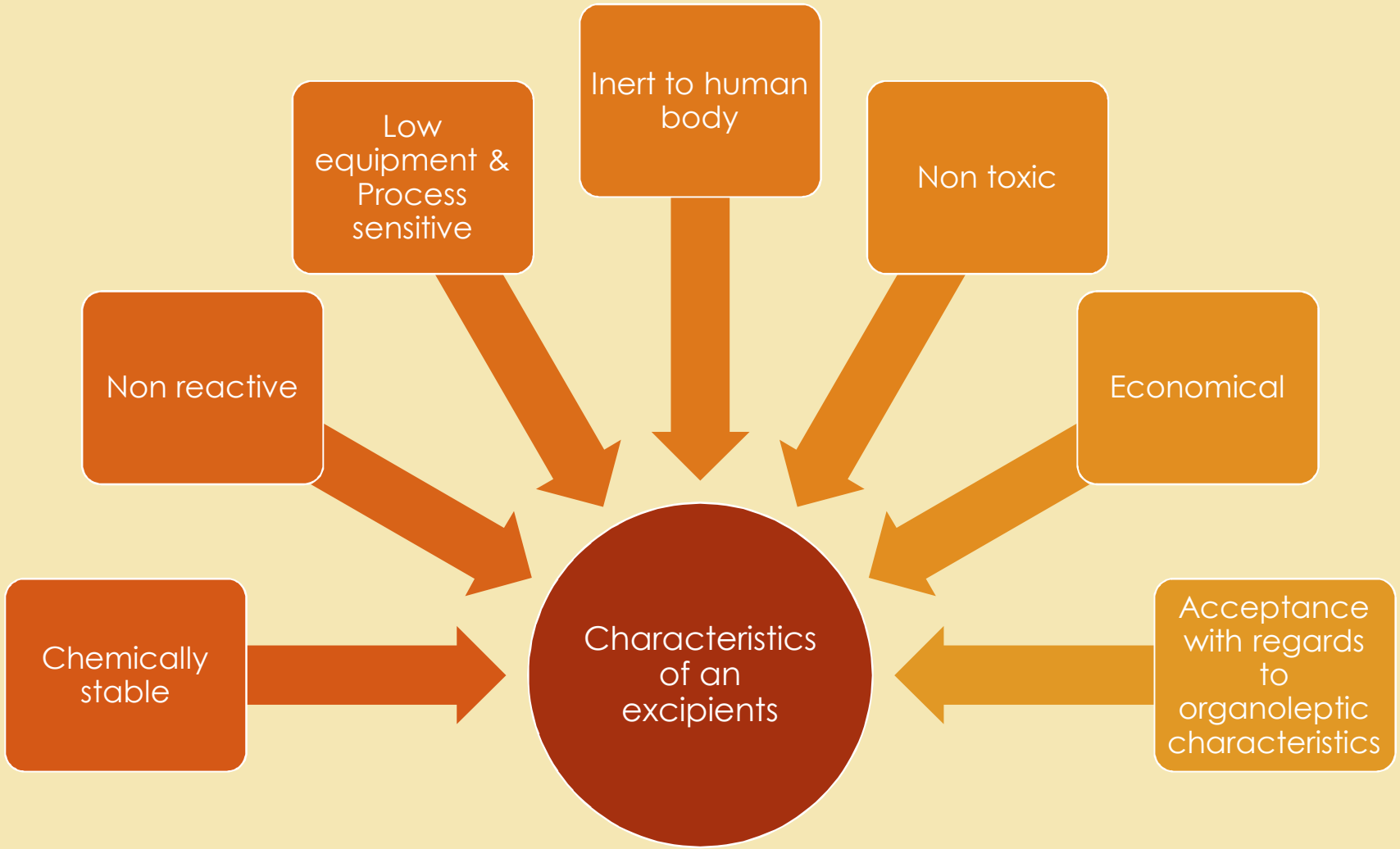
INTRODUCTION

- Pharmaceutical regulations and standards require that all ingredients in drugs, as well as their chemical decomposition products, be identified and shown to be safe. Often, more excipient is found in a final drug formulation than active ingredient, and practically all marketed drugs contain excipients.
- As with new drug substances and dosage forms thereof, novel excipients themselves can be patented; sometimes, however, a particular formulation involving them is kept as a trade secret instead (if not easily reverse-engineered).

EXCIPIENT BASED ON THEIR ORIGIN



IDEAL CHARACTERISTICS OF AN EXCIPIENTS



TYPES OF INTERACTIONS THAT AN EXCIPIANT CAN UNDERGO ARE:

- Drug-Excipient interactions
- Excipient-Excipient interactions
- Package-Excipient interactions

EXCIPIENT INTERACTIONS:

Drug-Excipient interactions

- In pharmaceutical dosage forms the active pharmaceutical ingredients are in intimate contact with the excipients which are in greater quantity. Excipients and drugs may have certain incompatibilities which lead to drug-excipient interaction.

Excipient-Excipient interactions

- Though observed very rarely, these are of prime importance in determining the stability of the dosage forms. Interactions can be undesirable as well as some interactions are used in the formulations to get the desired product attributes.

Package-Excipient interactions

- Packaging of pharmaceuticals is a vital part of the processing steps of product formulation, hence in pharmaceutical industry its essential that package selected adequately preserves the integrity of products, the selection of package therefore begins with a determination of products physical and chemical characteristics, its protective needs, and its marketing requirements.

5.4: THE QUALITY CONTROL REQUIREMENTS

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INTRODUCTION

- Tablets need to be strong enough to resist the stresses of packaging, shipping and handling by the pharmacist and patient.
- The mechanical strength of tablets is assessed using a combination of
  1. (i) simple failure and erosion tests.
  2. (ii) more sophisticated engineering tests.
- The simpler tests are often used for quality control purposes, whereas the more complex tests are used during the design of the formulation and manufacturing process in the research and development phase.

- Standards for tablet properties are published in the various international pharmacopeias (USP/NF, EP, JP, etc.).
- The hardness of tablets is the principle measure of mechanical strength. Hardness is tested using a tablet hardness tester. The units for hardness have evolved since the 1930s, but are commonly measured in kilograms per square centimeter. Models of tester include the Monsanto (or Stokes) Hardness Tester from 1930, the Pfizer Hardness Tester from 1950, the Strong Cob Hardness Tester and the Heberlain (or Schleeniger) Hardness Tester.

Common problems encountered during tablet manufacturing operations include:

Fluctuations in tablet weight, usually caused by uneven powder flow into the die due to poor powder flow properties.

Fluctuations in dosage of the Active Pharmaceutical Ingredient, caused by uneven distribution of the API in the tableting blend (either due to poor mixing or separation in process.

Sticking of the powder blend to the tablet tooling, due to inadequate lubrication, worn or dirty tooling, or a sticky powder formulation.

Capping, lamination or chipping. This is caused by air being compressed with the tablet formulation and then expanding when the punch is released: if this breaks the tablet apart, it can be due to incorrect machine settings, or due to incorrect formulation: either because the tablet formulation is too brittle or not adhesive enough, or because the powder being fed to the tablet press contains too much air (has too low bulk density).

Capping can also occur due to high moisture content.

General Appearance:

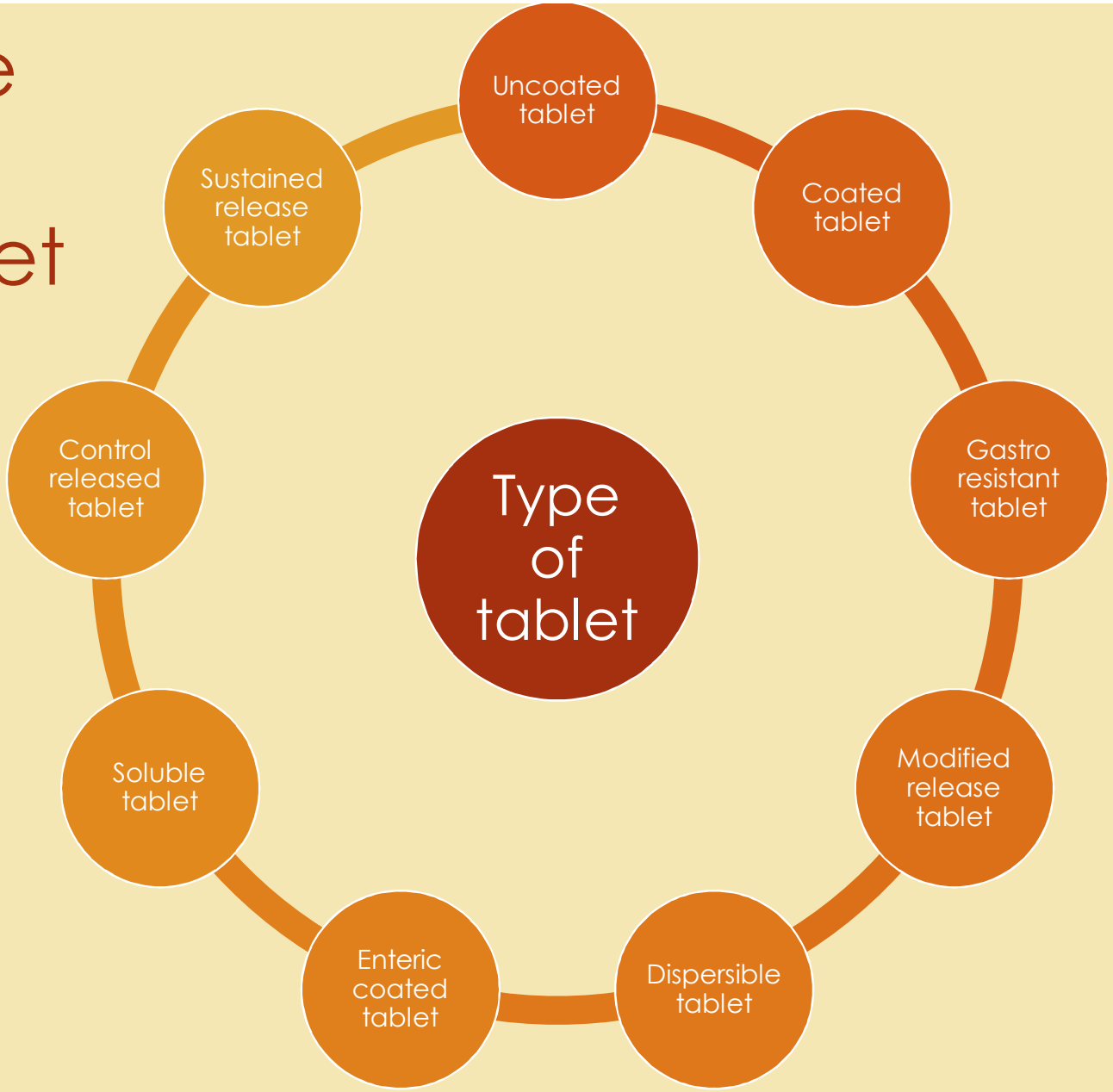
-Size, shape, and thickness:

This is important to facilitate packaging and to decide which tablet compressing machine to use.

-Organoleptic properties:

which include color and odor of the tablets.

Type of tablet



TEST INVOLVE IN TABLET QC

- Hardness
- Friability
- Disintegration
- Weight variation
- Dissolution test
- Granular strength
- Moisture content

HARDNESS TEST

Hardness (crushing strength):

- It is the load required to crush the tablet when placed on its edge.

Why do we measure hardness?

- *To determine the need for pressure adjustments on the tableting machine.*
- *Hardness can affect the disintegration. So if the tablet is too hard, it may not disintegrate in the required period of time. And if the tablet is too soft, it will not withstand the handling during subsequent.*

Amount of binder. (More binder a hardness)

Compression of the tablet and compressive force.

Method of granulation in preparing the tablet

Factors Affecting the Hardness:

FRIABILITY TEST

- *It is the tendency of tablets to powder, chip, or fragment and this can affect the elegance appearance, consumer acceptance of the tablet, and also add to tablet's weight variation or content uniformity problems.*
- Friability is a property that is related to the hardness of the tablet.
- An instrument called friabilator is used to evaluate the ability of the tablet to withstand abrasion in packaging, handling, and shipping.

DISINTEGRATION TEST

It is the time required for the tablet to break into particles, the disintegration test is a measure only of the time required under a given set of conditions for a group of tablets to disintegrate into particles.

WEIGHT VARIATION

- It is performed to check the uniformity of the tablet.

Dissolution

Å To check the percentage release from the dosage form.

Granular Strength

Å To determine the changes in the particles size distribution of granulation & compressibility.

Moisture content

Å Amount of moisture present in the granules.

TEST INVOLVE IN CAPSULES QC

- Disintegration
- Weight variation
- Dissolution test
- Content uniformity
- Moisture permeation test

EXPLAINATION:

DISINTEGRATION TEST:	• The disintegration test determines the whether capsules disintegrated with a prescribed time when placed in a liquid medium under the prescribed integral conditions.
WEIGHT VARIATION:	• To test the uniformity of weight of tablets and capsules • To ensure the consistency of dosage unit
DISSOLUTION	• To check the percentage release from the dosage form.
CONTENT UNIFORMITY	• To ensure that every dosage form contains equal amount of drug substance
MOISTURE PERMEATION TEST	• Preventing moisture from permeating through the packaging is an important function of the container-closure system used for medicines.

5.5: GRANULATION PROCESS

CHAPTER 5: FORMULATION OF SOLID DOSAGE FORM (TABLET & CAPSULES)

DEFINITION

Granulation is the process of collecting particles together by creating bonds between them. Bonds are formed by compression or by using a binding agent

REASON TO GRANULATE

- Improve flow
- Improve compression characteristics
- Improve the appearance of the tablet
- Improve content uniformity
- Decrease dust generation and reduce employee exposure to drug product

INTRODUCTION

- In the tablet pressing process, the main guideline is to ensure that the appropriate amount of active ingredient is in each tablet.
- Hence, all the ingredients should be well-mixed. If a sufficiently homogenous mix of the components cannot be obtained with simple blending processes, the ingredients must be granulated prior to compression to assure an even distribution of the active compound in the final tablet.
- Two basic techniques are used to granulate powders for compression into a tablet:
  1. Wet granulation.
  2. Dry granulation.
- Powders that can be mixed well do not require granulation and can be compressed into tablets through direct compression.

TYPES OF METHOD

- CONVENTIONAL METHOD
  - Wet granulation
  - Dry granulation
- ADVANCED METHOD
  - Fluidized bed granulation
  - Spray drying granulation
  - Freeze granulation

WET GRANULATION

Definition:

- Wet granulation is a process of using a liquid binder to lightly agglomerate the powder mixture. The amount of liquid has to be properly controlled, as over-wetting will cause the granules to be too hard and under-wetting will cause them to be too soft and friable.
- Aqueous solutions have the advantage of being safer to deal with than solvent-based systems but may not be suitable for drugs which are degraded by hydrolysis.

WET GRANULATION (Procedures)

- The active ingredient and excipients are weighed and mixed.
- The wet granulate is prepared by adding the liquid binder–adhesive to the powder blend and mixing thoroughly. Examples of binders/adhesives include aqueous preparations of cornstarch, natural gums such as acacia, cellulose derivatives such as methyl cellulose, gelatin, and povidone.
- Screening the damp mass through a mesh to form pellets or granules.
- Drying the granulation. A conventional tray-dryer or fluid-bed dryer are most commonly used.
- After the granules are dried, they are passed through a screen of smaller size than the one used for the wet mass to create granules of uniform size.

WET GRANULATION

- Low shear wet granulation processes use very simple mixing equipment, and can take a considerable time to achieve a uniformly mixed state.
- High shear wet granulation processes use equipment that mixes the powder and liquid at a very fast rate, and thus speeds up the manufacturing process.
- Fluid bed granulation is a multiple-step wet granulation process performed in the same vessel to pre-heat, granulate, and dry the powders. It is used because it allows close control of the granulation process.

ADVANTAGES & DISADVANTAGES

Improve flow ability and compressibility of the material.	An expensive process.
Fast method to prepare controlled release granules.	Process loss of material was high.
Improve homogeneity of dosage form.	Unsuitable for moisture sensitive, thermo-labile.

DRY GRANULATION

Definition:

- Dry granulation processes create granules by light compaction of the powder blend under low pressures. The compacts so-formed are broken up gently to produce granules (agglomerates). This process is often used when the product to be granulated is **sensitive to moisture and heat**.
- Dry granulation can be conducted on a tablet press using slugging tooling or on a roll press called a roller compactor. Dry granulation equipment offers a wide range of pressures to attain proper densification and granule formation.
- Dry granulation is simpler than wet granulation, therefore the cost is reduced. However, dry granulation often produces a higher percentage of fine granules, which can compromise the quality or create yield problems for the tablet. Dry granulation requires drugs or excipients with cohesive properties, and a 'dry binder' may need to be added to the formulation to facilitate the formation of granules.

ADVANTAGES & DISADVANTAGES

Improved flow by increasing particle size.	Increases the potentiality of cross contamination.
Granulation without of any liquid.	Does not permit uniform color distribution.
Required less energy.	Tends to create more dust.

GRANULE LUBRICATION

- After granulation, a final lubrication step is used to ensure that the tableting blend does not stick to the equipment during the tableting process.
- This usually involves low shear blending of the granules with a powdered lubricant, such as magnesium stearate or stearic acid.

5.6: DRYING PROCESS

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INTRODUCTION

- Drying is a most important step in the formulation and development of pharmaceutical product.
- It is important to keep the residual moisture low enough to prevent product deterioration and ensure free flowing properties.
- The commonly used dryer includes **Fluidized bed dryer**, **Vacuum tray dryer**, **Microwave dryer**, **Spray dryer**, **Freeze dryer**, **Turbo - tray dryer**, **Pan dryer.**

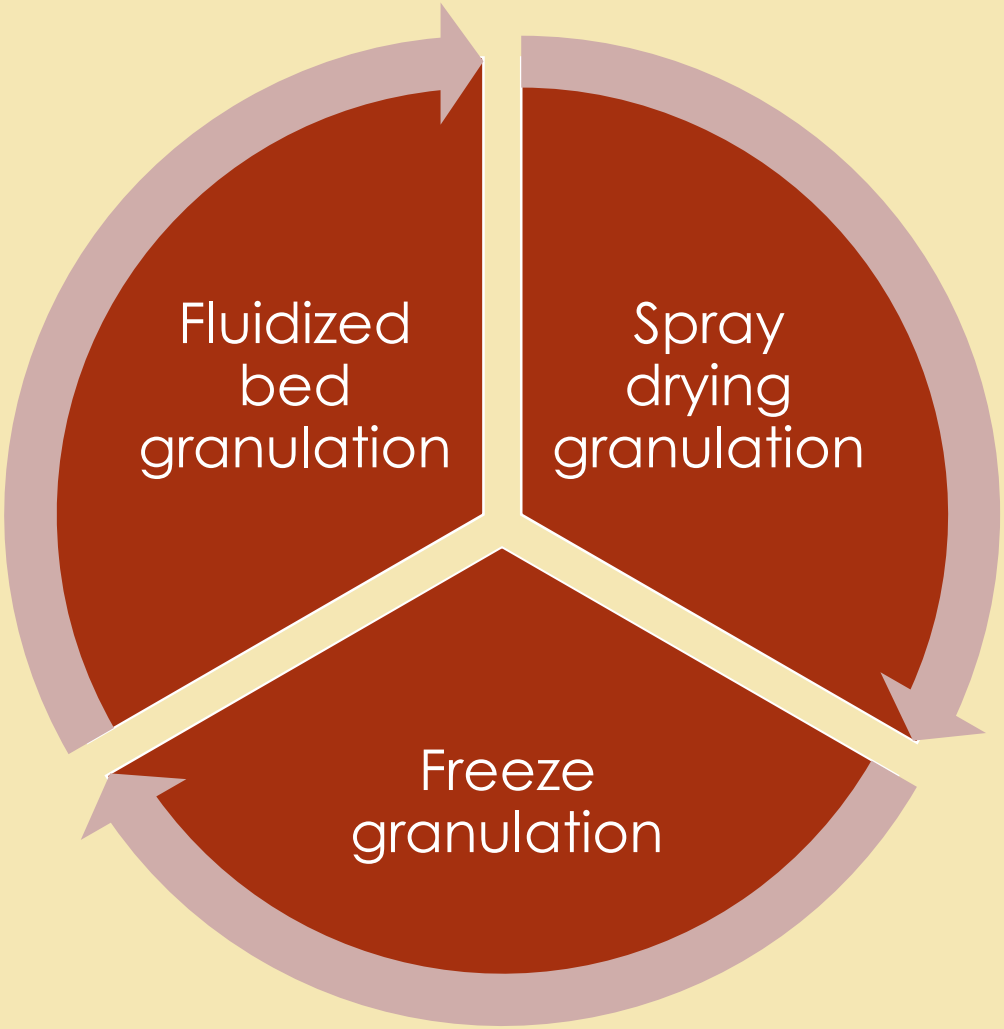
INTRODUCTION

DRYING PROCESS:

A process of evaporating the liquid contained within aggregates produced by a wet granulation process to a predetermined moisture content

Process: To reduce the moisture level of wet granules

ADVANCE METHOD



1) Fluidized bed dryer (Process)

- Hot air passed at high pressure through a perforated bottom of the container containing granule to be dry
- The granule are lifted from the bottom and suspended in the stream of air
- This is called fluidized state

Advantages

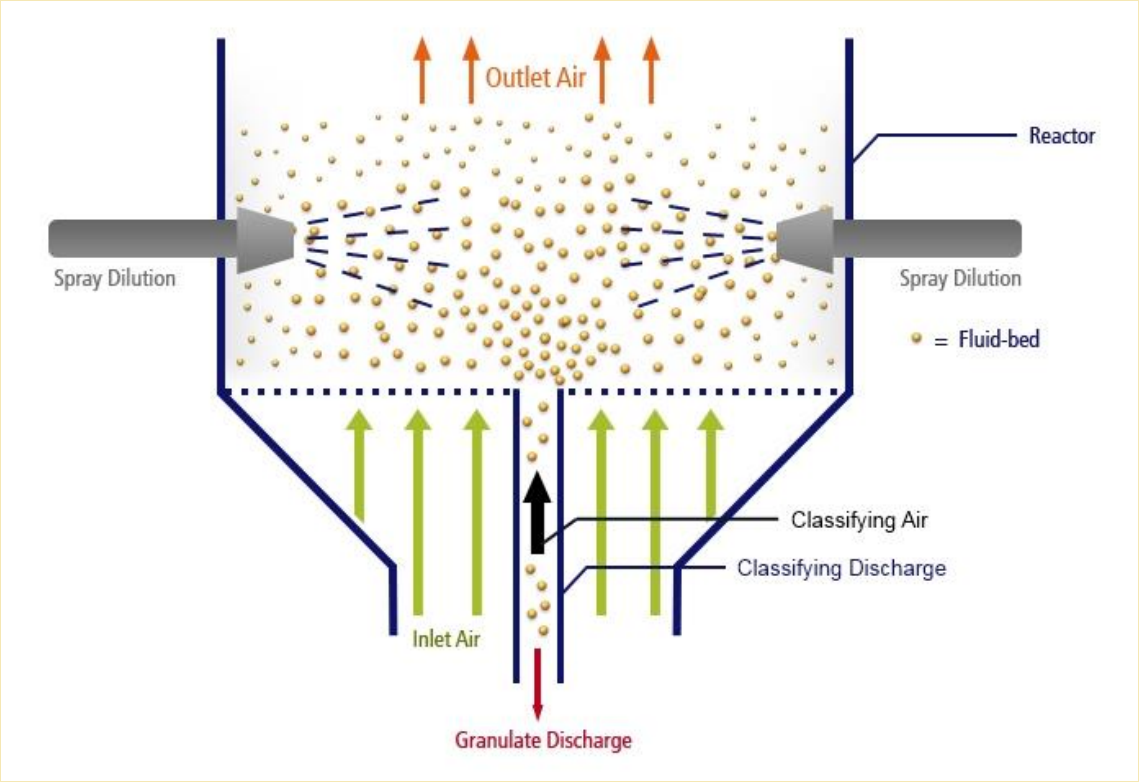
- Reduce dust formation
- Improve house keeping and workers safety.

Disadvantages

- Cleaning was label intensive and time consuming.
- Assuring reproducibility was troublesome.

2) Spray drying granulation

- Liquid feed is pumped through an atomizer device that produces fine droplets into the main drying chamber.



Advantages

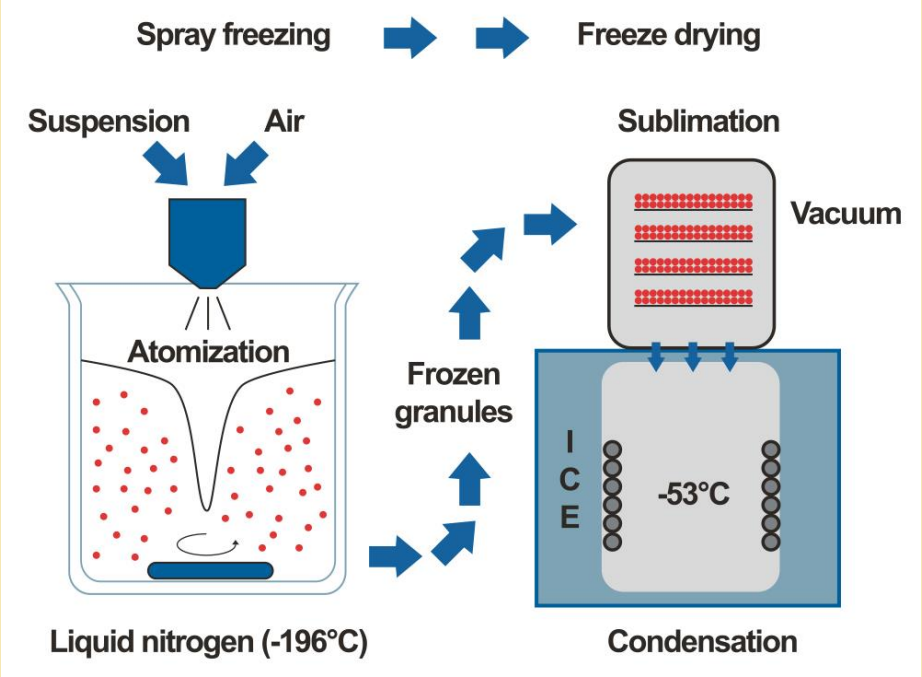
- A rapid and continuous proces
- Suitable for heat sensitive product
- Cost effective

Disadvantages

- High installation cost
- Solid materials cannot be dry
- Equipment is bulky, cleaning is time consuming

3) Freeze granulation

- Initial liquid solution or suspension is frozen and the water is remove by sublimation.



Advantages	Disadvantages
Equipment can be easily clean up	Need for sterile diluents upon reconstitution
Organic solvent can be recycle	Increase handling and processing time
High yield with low material waste	High cost equipment

SUMMARY

- A tablet is a pharmaceutical dosage form. It comprises a mixture of active substances and excipients, usually in powder form, pressed or compacted from a powder into a solid dose.
- The use of hard shell capsules is a popular drug delivery method. In the hard shell capsule delivery method, dry ingredients are encapsulated by filling and closing a two piece protective shell, typically made of gelatin, vegetable or cellulose polymers.

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