Pharmaceutical Excipients

BY

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Pharmaceutical excipients are any substance other than the active drug or prodrug
that has been appropriately evaluated for safety and is included in a drug
delivery system to either aid processing of the system during manufacture, or protect,
support or enhance stability, bioavailability or patient acceptability, or assist
in product identification, or enhance any other attribute of the overall safety and
effectiveness of the drug product during storage or use (

WHAT IS EXCIPIENT ?

•The term comes from Latin word "excipiens" which means to receive or to take out.

" IT IS AN INERT SUPPORT OF THE ACTIVE PRINCIPLE "

•According to International Pharmaceutical Excipient Council (IPEC):

These are the process aids or any substances other then the Active Pharmaceutical Ingredient (API) or prodrug that is included in pharmaceutical dosage forms.

Excipients can be considered to be the ‘‘Cinderellas’’ of formulation science and drug delivery. They do not treat the disease, nor should they have a pharmacological effect of their own (although they may exert a physiological effect). However, an understanding of the reasons for their presence in the formulation and how they are used is key to the design of robust, reliable medicines that deliver the drug to the patients in the correct amount, at the correct rate, throughout their shelf-life, consistently batch after batch.

1. They must be nontoxic and acceptable to the regulatory agencies in all countries where the product is to be marketed.
2. They must be commercially available in an acceptable grade in all countries where the product is to be manufactured.
3. 'lheir cost must be acceptably low.
4. They must not be contraindicated by themselves (e.g., sucrose) or because of a component (e.g., sodium) in any segment of the population.
5. They must be physiologically inert.

6. They must be physically and chemically stable by themselves and in combination \ dth the drug(s) and other tablet components.
7. They must be free of any unacceptable microbiologic "load."
8. They must be color-compatible (not produce any off-color appearance).
9. If the drug product is also classified as a food, (certain vitamin products), the diluent and ot rer excipients must be approved direct food additives.
10. They must have no deleterious effect on the bioavailability of the drug(s) in the product.

Classification of Excipients

1. Excipients for use in oral Medicines.
   a. Excipients used in solid dosages form.
   b. Excipients used in liquid dosage forms.
   c. Excipients used in semi solid forms.
2. Excipients used for porenterals.
3. Excipients used in topical drug delivery systems.
4. Excipients used in Intranasal and Intralation delivery systems.

Ideal characteristics….

- Nontoxic
- Pharmacologically inert.
- Physically and chemically stable.
- Acceptable to the Regulatory agencies in all countries.
- Commercially available.
- Have pleasing organoleptic properties.
- Must be colour compatible.
- Economical

Basic requirements of a modern pharmaceutical Excipients:

➢ API vs. Excipients:

- ✓ *For both safety and quality.*
- ✓ *For API therapeutic efficacy.*
- ✓ *For Excipients functionality.*

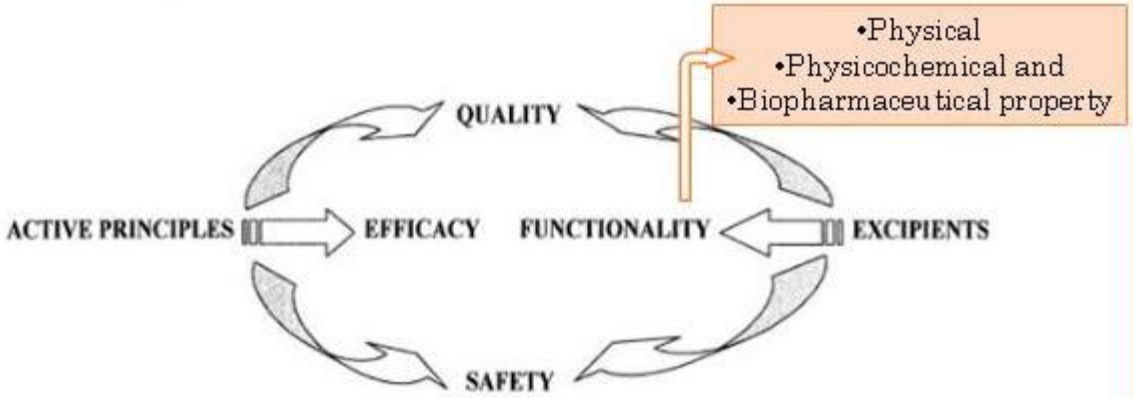


Fig. 1. Main requirements for pharmaceutical excipients.

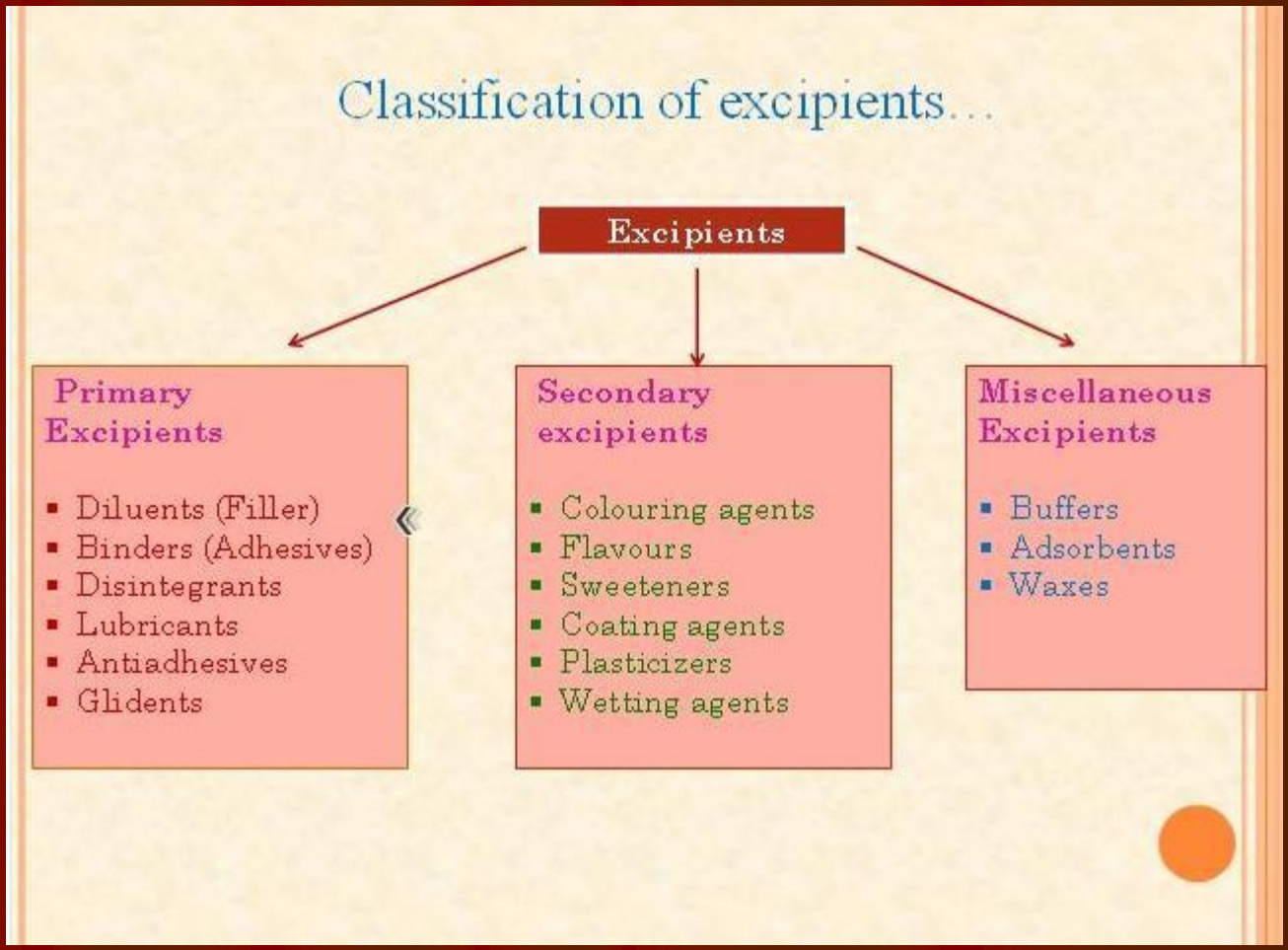
What are the functionalities of Excipient?

- Impart weight, consistency and volume:

  It's allow accuracy of dose.

- Improve solubility.
- Increase stability.
- Enhance bioavailability.
- Modifying drug release.
- Assist in product identification.
- Increase patient acceptability.
- Facilitate dosage form design.

Classification of excipients…



Diluents (Filler):

- Diluents are used to increase the bulk volume of a tablet or capsule when the drug dosage itself is inadequate to produce tablets of adequate weight and size.

- Usually the range of diluent may vary from 5-80%.

- The tablet size should be kept above 2-3 mm.
- Minimum tablet weight is typically ~50mg.
- Actual API doses can be as low as ~20µg.

❖ Functions of diluent:

- To facilitate tablet handling during manufacture.
- To achieve targeted content uniformity.
- To provide improved cohesion.
- To allow direct compression manufacturing.
- To enhance flow.
- To adjust weight of tablet as per die capacity.

Classification of diluents…

Four major classes:

➢ Natural Diluents:

- Starch
  - Native starch (PharmGel, StarCap 1500, Sta-Rx 1500)
  - Hydrolyzed starch (Emdex, Celutab)
  - Partially pregelatinized starch (Lycatab)
- Soyabean powder (newly introduced)

➢ Organic Diluents:

- Lactose
  - α-lactose monohydrate (trade name Pharmatose and Respitose).
  - Spray dried lactose (Spray Process 315)
  - Anhydrous lactose (Pharmatose DCL 21)
- Sucrose (Sugartab, Dipac, Nu tab)
- Mannitol (Parteck M, Pearlitol)
- Sorbitol (Sorbifin, Sorbidex and Neosorb)
- Xylitol (Xylisorb- used in chewable tablets)
- Erythritol (Zerose)
- Powdered cellulose (Elcema G-250)
- Microcrystalline cellulose (Avicel- [PH 101, 102, 105], Emcocel, Tabulose)

Inorganic Diluents:

- Dibasic calcium phosphate dihydrate (Di-Tab, Emcompress)
- Dibasic calcium phosphate anhydrate (A-Tab, Fujicalin)
- Tribasic calcium phosphate (Tri-Tab)

•The inorganic diluents, do not exhibit binding properties when used in wet granulation and direct compression.

Co-processed Diluents:

- Co-processing means combining two or more materials by an appropriate process. It provide better tableting properties than a single substance.

According to solubility in water:

INSOLUBLE DILUENTS	SOLUBLE DILUENTS
Starch	Lactose
Powdered cellulose	Sucrose
Microcrystalline cellulose	Mannitol
Calcium phosphates, etc.	Sorbitol, etc.

TRADE NAME OF DILUENTS	COMPOSITION
Fast Flo lactose	Crystalline α-lactose monohydrate and amorphous lactose.
Microcellac	75% lactose and 25% MCC
Ludipress	93% α-lactose monohydrate, 3.5% polyvinylpyrrolidone, and 3.5% crospovidone.
Nu-Tab	Sucrose 95-97%, invert sugar 3-4% and magnesium- stearate 0.5%
Di-Pac	Sucrose 97% and modified dextrins 3%
Sugartab	Sucrose 90-93% and invert sugar 7-10%.
Emdex	Dextrose 93-99% and maltose 1-7%
Cal-Tab	Calcium sulfate 93% and vegetable gum 7%
Cal Carb	Calcium carbonate 95% and maltodextrins 5%
Calcium 90	Calcium carbonate 90-91% and Starch 9-10%

Binders (Adhesives)

- Binders are used to hold the active pharmaceutical ingredient and inactive ingredients together in a cohesive mix. (5-25%)

Binders ensure the mechanical strength.

Exhibit cohesive and adhesive force.

Classification of binder:

➢ **According to their application:**

- **Dry binders :**

  Direct powder compression.
  Dry granulation (roller compaction, slugging).

- **As a solution or paste:**

  Wet granulation

➢ **Granulating fluid used:** Water and occasionally with ethanol.

➢ **According to their solubility:**

- Insoluble in water e.g. starch
- Soluble in water e.g. HPMC
- Soluble in water and ethanol e.g. Povidone

➢ **According to their chemical source:**

- **Saccharides and their derivatives:**
- **Disaccharides:** sucrose, lactose
- **Polysaccharides and their derivatives:**

  Starches: Starch paste, pregelatinized starch.

  Modified cellulose: microcrystalline cellulose.

  Cellulose ethers: hydroxypropyl cellulose, HPMC.

  Sugar alcohols: xylitol, sorbitol etc.
- **Naturl gums:** acacia, tragacanth.
- **Protein:** gelatin
- **Synthetic polymer:** polyvinylpyrrolidone(PVP), polyethyiene glycol

DISINTEGRANT AND SUPER-DISINTEGRANT

- Disintegrants cause rapid break up of the tablet compact upon exposure to moisture.
- Super disintegrant: the simplest way to achieve quick disintegration
- Used intragranulerly or extragranularly or both for better action.

➢ Mode of action:

- Swelling : e.g.- Cellulose and its derivatives
- Porosity and Capillary Action (Wicking): e.g.- Microcrystalline cellulose
- Deformation
- By enzymatic reaction: enzymes destroy the binding action of binder and helps in disintegration.

ENZYMES	BINDER
Amylase	Starch
Protease	Gelatin
Cellulase	Cellulose derivatives
Invertase	Sucrose

Types of disintegrant:

BRAND NAMES	CONC. IN %	CATEGORIES
Starch USP	5-20	Native starch
Starch 1500	5-15	Modified starch
Avicel (PH 101, PH 102)	10-20	Microcrystalline cellulose
Solka floc	5-15	Purified wood cellulose
Alginic acid NF	1-5	Acts by swelling
Na alginate	2.5-10	Acts by swelling
Explotab, Primojel	2-8	Sodium starch glycolate, (superdisintegrant)
Polyplasdone (XL)	0.5-5	Crosslinked PVP
Amberlite (IPR 88)	0.5-5	Ion exchange resin
Methyl cellulose, Na CMC, HPMC	5-10	Cellulose derivatives
AC-Di-Sol	1-3	Direct compression
Polyplasdone		Miscellaneous category

LIST OF SUPERDISINTEGRANTS

SUPERDISINTEGRANTS	EXAMPLE OF	MECHANISM OF ACTION
Crosscarmellose Ac-Di-Sol Vivasol Primellose	Crosslinked cellulose	-Swells 4-8 folds in < 10 seconds. -Swelling and wicking both.
Crosspovidone Crosspovidon M Kollidon Polyplasdone	Crosslinked PVP	-Swells very little and returns to original size after compression but act by capillary action
Sodium starch glycolate Explotab Primogel	Crosslinked starch	-Swells 7-12 folds in <30 seconds
Alginic acid NF Satialgine	Crosslinked alginic acid	-Rapid swelling in aqueous medium or wicking action
Soypolysaccharides Emcosoy	Natural super disintegrant	Swelling
Calcium silicate		-Wicking action

LUBRICANTS, ANTIADHESIVES AND GLIDENTS

Lubricants are used in formulations to:

- Smooth ejection of tablet from die cavity.
- Prevent sticking of powder on punch faces.
- Reduce interparticle friction during compression.
- Improve flow of powder blend and granules into the die cavity.

- **Usual range (0.1-5%)**
- **Under-lubricated blends - compression sticking problems.**
- **Over-lubricated blends - adversely affect tablet hardness and dissolution rate.**

- **According to functionality:**

(1) **Glidant**: enhance flow property of powder blend by overcoming powder cohesiveness.

(2) **Antiadherent:** prevent sticking to the punch.

(3) **Die wall lubricant:** reduce the friction between the tablet surface and the die wall during and after compaction to enable easy ejection.

➢ **Die-wall lubricants are of two classes:**

- **Fluid lubricants:** work by separating moving surfaces completely with a layer of lubricant.
- **Boundary lubricants:** work by forming a thin solid film at the interface of die and tablet.

➢ **According to solubility:**

- **Hydrophobic:** Most widely used lubricants in use today.
- **Hydrophilic:** Generally poor lubricants, no glidant or anti-adherent properties.

HYDROPHILIC	HYDROPHOBIC
Boric acid	Magnesium, calcium and sodium stearate
Sodium chloride	Stearic acid
DL- Lucine	Sterotex
Carbowax 4000, 6000	Sterowet
Sodium lauryl sulfate	Aerocil

CATEGORIES	CONCENTRATIONS USED IN %
Glidant	
Talc	1-5
Fumed silicon dioxide	0.1-0.5
Native starch	1-10
Aerosil	1-3
Antiadherent	
Talc	1-5
Cornstarch	3-10
Cab-O- Sil (Fumed Silicon Dioxide)	0.1-0.5
Syloid	0.1-0.5
DL- Leucine	3-10
Fluid lubricants	
Light mineral oil	1-3
Vegetable oils (Sterotex, Lubritab)	2-5
Glyceryl Behenate (Compitrol 888)	
Boundary lubricants	
Metallic stearate	0.2 - 2
Sodium stearyl fumarate	0.5 - 2
Polyethylene glycol	2 - 20
Sodium lauryl sulfate	1 - 3

COLOURING AGENTS

Colours are incorporated into tablets generally for :

- Identification of similar-looking products.
- Minimize the possiblity of mixups.
- Increase aesthetic value or their marketing value.

- FD&C and D&C dyes and lakes are mostly used.

Dyes are relatively unstable because :

1) light sensitive
2) By oxidizing and reducing agents
3) Microorganisms
4) Trace metals
5) pH
6) High temperatures.

COLOURS	COMMON NAMES
FD&C blue #1	Brilliant blue FCF
FD&C blue #2	Indigotine
D&C blue #4	Alphazurine
D&C blue #9	Indanthrene blue
FD&C green #3	Fast green FCF
D&C green #5	Alizarin cyanine green F
D&C green #6	Quinizarine green SS
D&C green #8	Pyranine concentrated
D&C orange #4	Orange II
D&C orange #5	Dibromofluorescein
D&C orange #10	Diiodofluorescein
FD&C red #3	Erythrosine
FD&C red #4	Ponceau
D&C red #7	Lithol rubin
D&C red #17	Toney red

FLAVORS AND SWEETENERS

- Flavors and sweeteners are commonly used to improve mouth feel
- Flavors have found little acceptance due to their lesser stability upon aging

Types of flavor:

Water soluble (solution)
Volatile oils
Dry flavors

e.g.:-

- Bitter product - mint, cherry or anise may be used.
- Salty product - peach, apricot or liquorice may be used.
- Sour product - raspberry or liquorice may be used.
- Excessively sweet product - vanilla may be used.

COATING AGENTS:

COATING TYPE	POLYMERS	TRADE NAME
Enteric Coatings	• Cellulose Acetate Phthalate • HPMC	• Aquacoat CPD • Sepifilm LP
Polymer Extenders	• Hydroxypropylcellulose	• Klucel EF and LF
Immediate Release Coatings	• HPMC • Ethylcellulose • Microcrystalline Cellulose • Carrageenan • Methylcellulose	• Sepifilm LP • Aquacoat ECD • Lustre Clear • Metolose SM-4
Sustained Release Coatings	• Ethylcellulose	• Aquacoat ECD • Aqualon
Subcoat	• Hydroxypropylcellulose	• Klucel
Pellet Coating	• Methylcellulose	• Metolose SM-4

PLASTICIZERS FOR COATING

✓Used for physical modification of coating polymer.

- Plas II: composed of: Glyceryl Monostearate
  Polysorbate 80
  Triethylcitrate
  Methyl Parabens
  Propyl Parabens

- Citrate Esters
- Triethyl citrate
- Acetyltriethyl Citrate
- Acetyltri-n-butyl Citrate
- Dibutyl Sebacate
- Diethyl phthalate
- Triacetin

Miscellaneous components

BUFFERS (Maintain a required pH for stability)
Sodium bicarbonate
Sodium citrate
Calcium carbonate

ADSORBENTS
Silicon dioxide (Syloid, Cab-O- Sil, Aerosil)
Bentonite
Kaolin
Magnesium silicate
Tricalcium phosphate
Magnesium carbonate
Magnesium oxide

WAXES (Polishing agent)
Caranauba
Yellow Beeswax
White Beeswax
Paraffin
Naphtha

Physicochemical Tests for Excipients

- Flow rate
- Gel strength (binders)
- Lubricity (frictional)
- Microbiological status
- Moisture sorption
- Particle hardness
- Particle size distribution:
  - (1) sieve analysis
  - (2) air permeability

- Porosity
- Shear rate
- Tensile strength
- Bulk volume
- Water absorption


THANK YOU