

# Excipients – Functionality Specifications and Monographs



**S D Joag**

**Hon Gen Secretary, IPA**

**Director, Dr. M K Rangnekar Lab,  
Mumbai**

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**At**

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# Excipients



- Pharmaceutical excipients are substances other than API/APIs, or prodrug that are included in a finished pharmaceutical dosage form [IPEC]
- **Origin**
- **ex·cip·i·ent** (k-sp-nt) : Noun  
An inert substance used as a diluent or vehicle for a drug.
- [Latin **excipins, excipient-**, present participle of **excipere, to take out, exclude; see except.**]

# Excipients



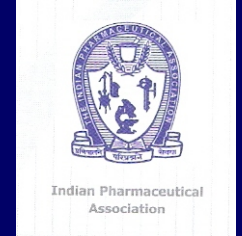
- Excipients are used in virtually all drug dosage forms.
- They are essential to product performance.

# Excipients



- Product performance and functionality of excipient are two sides of the same coin and are inter-dependable
- Right choice of the excipient/s makes the product stable, safe and effective and makes it superior than other products
- Thus the formulation of excipients in many cases is considered a trade secret

# Some of the known Functional Categories of Excipients



Diluent / Filler

Lubricant

Surfactant (Emulsifying, Wetting and Solubilising Agent )

Binder

Colorants

Suspending / Viscosity increasing Agents

Sweetening Agents

Glidant and or Anticaking Agents

Coating Agents

# Some of the known Functional purposes of Excipients



Vehicle – Pharmaceutical Water

Tonicity Agent

Plasticizers

Suppository Base

Ointment Base

Buffer

Disintegration

Flavors

Preservatives

Anti-oxidants

# Excipient Origins

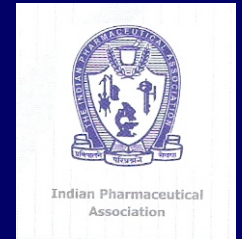


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- From deep in the Earth
- Soil

# Excipient Origins



- From crude oil to refined stage
- Petroleum
- Poly-glycols
- Starting materials for synthetic Chemistry

# Excipient origins

## Agriculture : Wheat, Corn, Sugar Cane, Cotton etc.



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# Tallow oils to glycerin and fatty acids



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# Agriculture derived excipients

- Maize, , Potato, Wheat, Starches
- Sugar (Beet, Sugarcane)
- Dextrins
- Cyclodextrins
- Sorbitol
- Glycerin



# Minerals & Natural origin

- Talc
- Kaolin
- Sodium chloride ( Sea Water)
- Silicon Dioxide ( Silica - Aerosil)
- Calcium Carbonate (Oyster Shell)

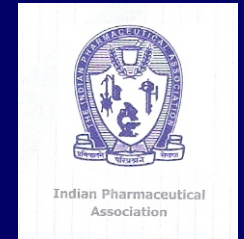
# Processes



From very simple to complex e.g.

- Talc: mining -- drying -- milling
- Sugarcane -- Refined sugar
- Sorbitol -- Maize -- 20 steps -- Sorbitol
- Bones -- Gelatin (Animal Based)
- Tallow oils -- glycerin and fatty acids

# Excipients



- A very diverse collection of materials
- About 1200 ingredients are in use currently in marketed pharmaceutical products as excipients excluding colors and flavors
- About 250 documented in the European Pharmacopoeia
- Now 60 monographs in the international harmonization process, USP, JP and Ph Eur

# Excipients



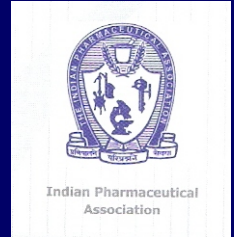
- Successful manufacture of robust product requires well-defined excipients and processes.
- Pharmacopoeial Monographs:
  - 14 out of 40 functional categories identified in USP 30 - NF 25
  - EP (EDQM) plans to list specific functionality related characteristics in some of its excipient monographs

# USP General Chapters useful for formulators for consistent excipient performance



- <616> Bulk and Tapped density**
- <695> Crystallinity**
- <699> Density of solids**
- <731> Loss on Drying**
- <786> Particle size distribution- sieving**
- <846> Specific surface area**
- <911> Viscosity**

# Pharma use of Excipients



Contrary to APIs, excipients are not specifically made for use in medicinal products e, g.

- Cellulose
- Propellants
- Sugar
- Glycerin
- Starch
- Colors
- Flavors

# Types of Excipients

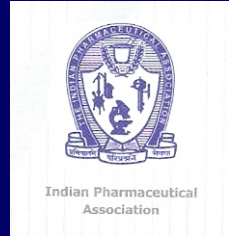


Excipients also in use as API: usually one pharma grade is made e.g.

Di-calcium Phosphate, Calcium Carbonate

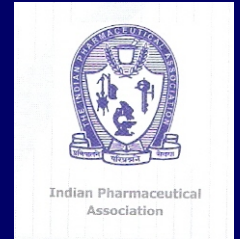
Excipients developed and manufactured specifically for pharma use: special grade or grades

# Excipient grade considerations



- Material should be fit for its intended use
- Food grade material usually acceptable for (oral) pharma use, however consider : functionality, interactions, stability issues due to inconsistency in quality
- Special grades needed for parenterals, inhalation and speciality products

# Impurities in Excipients



## Issues with Excipient/s

Source

Quantity in formulation

Purity / Grade

Interactions with other excipient/s

Degradation during shelf-life of the product

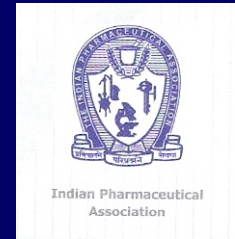
# Impurities in Excipients



- General
  - impurities related to starting materials
  - manufacturing processing aids
  - Contaminants – storage, packing,

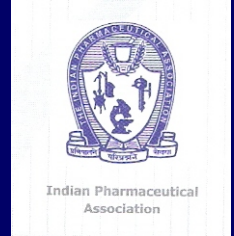
To be controlled by GMP

# Impurities in Excipients



- Definition of the material: single or multiple component substance
- Related substances from the starting materials, the process or instability
- Additives, components added intentionally

# Impurities in Excipients



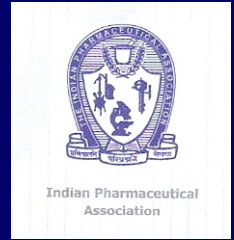
- Organic impurities
- Inorganic impurities
- Residual solvents
- Pesticides, anti-fungals
- Microbial contamination

# Pharmacopoeial Excipients



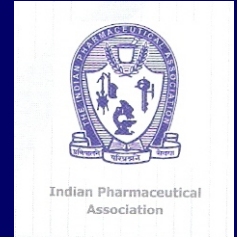
- Monograph in general sufficient to distinguish technical grades from pharma
- Monograph represents acceptance criteria for general use
- Debate on functionality related characteristics on going
- 14 high-priority functional categories have been identified in USP 30 – NF 25

# Pharmacopoeial Excipients, issues



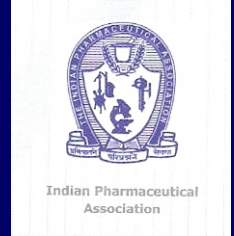
- Genotoxic impurities
- Heavy metals (residues of catalysts)  
Heavy metals test not satisfactory
- Mycotoxins

# Some examples



- Inorganic impurities
- Heavy metals in
  - minerals
  - Hydrogenated fats
  - Gelatin, Acacia,
  - Stearates
  - Polymers
  - Liquids (containers)

# Non pharmacopoeial excipients



- Well known substances:  
reference to literature
- Novel excipients:  
Stringent Regulatory requirements for approval

follow ICH guidance as for API  
but look for quality, safety and functionality

# Some examples



- Inorganic impurities
- sulfites processing aid starches and refined sugars
- radioactive nuclides

# Some examples



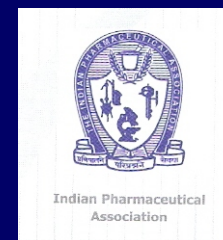
- Organic impurities
- proteins e.g. gluten, prion, protein
- additives e.g. Silicon dioxide
- BHT/BHA
- Tocopherol
- Hydrogen peroxide

# Some examples



- Organic impurities:
- monomers and processing aids in polymers, special instructions on ethylene oxide residues
- residual solvents
- pesticides

# Some examples



## Organic impurities

- microbial contamination
- mycotoxins
- residues from antimicrobial treatment

# Excipients

## Critical Considerations

### Challenges for Formulators



- Disintegration
- Dissolution/BA-BE
- Content uniformity
- Sustained / Delayed Release consistency
- Stability – Climatic conditions
- Patient compliance

# Conclusions



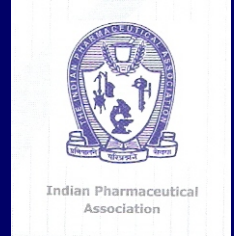
- Definition of substance composition, very important**
- **Knowledge of origin and main use of the Excipient**
- **Apply general ICH guidance philosophy for novel materials**
- **Strictly adhere to monograph specifications**
- **Devise additional functionality tests and specifications as in-house**

# Questions to be asked



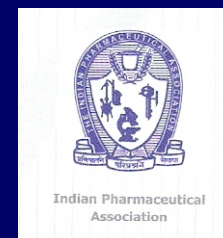
- What is excipient?  
A Commodity, a very special product, main use in the world, grades available?
- Who is the provider?  
A manufacturer, a distributor, a trader, a broker...?
- Is the provider a specialist in the pharma world?

# Security



- What are the credentials of the provider?
- What kind of quality system is in place?
- What is the capacity to provide stable quality in the amounts necessary

# Openness



- Is the provider open to discuss - under confidentiality agreement particulars of the ingredient, the manufacturing process
- Is the provider open to audit?
- Is the provider interested in co-development of improved quality better performing ingredients ?



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Thank You