# Unit-1
# Preformulation Concepts

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# Drug Excipient Interaction

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# Objective of Preformulation Studies

- Formulate Stable Formulation and
- Bio available dosage form

# Introduction

## Pharmaceutical Excipients

An excipient is a pharmacologically inactive substance formulated alongside the API of a medicine to impart specific qualities to them.

## Role of Excipients

- ✓ Provide bulk to the formulation
- ✓ Protect, support or enhance the stability of formulation.
- ✓ Improve bioavailability of drug

# Drug Excipient Interaction

Drug substances are usually in intimate contact with excipient. Although these are pharmacologically inert, they can undergo chemical and physical interaction with drug substance under favourable condition. These interactions can lead to instability resulting in the formulation of new entities.

# Importance of Drug Excipient Compatibility Studies

- ✓ To find out how compatible an excipient is with API
- ✓ Maximizes the stability of a dosage form.
- ✓ Determine the list of excipient that can be used in final dosage form.
- ✓ Helps to avoid surprise problem during formulation process
- ✓ These studies are the part of preformulation study and this study data is essential for IND submission.

# Mechanism Of Drug Excipient Interaction

- They can be classified as-

Physical interaction

Chemical interaction

Biopharmaceutical interaction

# 1. Physical Interaction

These are very common in dosage form and also difficult to detect. These involve change in –

- ✓ Dosage uniformity, color, odor, dissolution, stability or sedimentation rate etc.
- ✓ These interactions can either be beneficial or detrimental to the product performance.

Eg. of some these interactions are as follows –

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# Physical Interaction

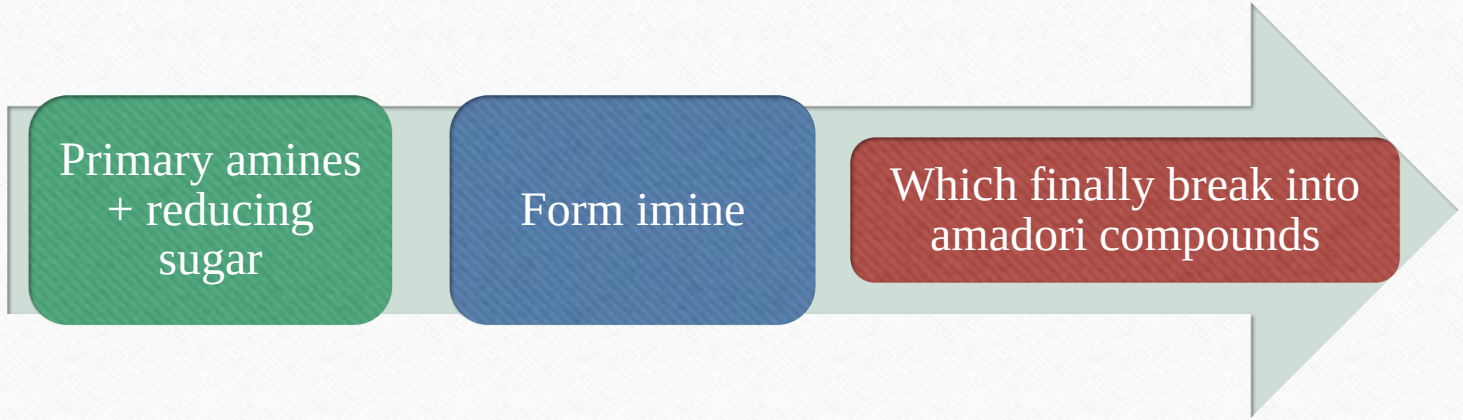
| Interaction | Beneficial effect example | Detrimental effect example |
|---|---|---|
| 1.Complexation | Cyclodextrin | • Tetracycline<br>• Formulation of chlorpromazine with tween 80 and SLS |
| 2. Adsorption | Formulation of Indomethacin (NSAID) using kaolin as adsorbent | Formulation of Cetyl Pyridinium chloride tablets using magnesium stearate as a lubricant |
| 3.Solid dispersion | Formulation of Piroxicam, Norfloxacin, Nifedipine and Ibuprofen using PEG of different grades | Interaction between Povidone and stearic acid in a capsule |

# 2.CHEMICAL INTERACTION

Chemical interaction involves chemical reaction between drugs and excipients or drugs and impurities/ residues present in the excipients to form different molecules. Chemical interactions are almost detrimental to the product because they produce degradation products. They are as follows-

**1.Chemical interactions between drug and excipients-** Eg are as follows-

- Maillard reaction- eg chlorpheniramine and dextrose interaction

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- Release of diclofenac sodium from matrix tablet was inhibited by polymer chitosan at low pH, due to formation of ionic complex between diclofenac sodium and ionized cationic polymer

- Sodium alginate dissolve in water to form large negatively charged anions, co-formulation in aqueous systems with drugs such as neomycin and polymixin (positively charged) result in precipitation.

**2. Interaction of drug with excipient residues/ impurities-**

- Excipients are not exquisitely pure. They have some residues which affect the drug action.
- **Impurities found in common excipients-**

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| Excipient | Residue |
|---|---|
| Povidone, Polysorbates | Peroxides |
| Magnesium stearate | Antioxidants |
| Lactose | Aldehydes, reducing sugars |
| Benzyl alcohol | Benzaldehyde |

- Sterilization by autoclaving of parenteral preparations containing dextrose can cause isomerization of dextrose in fructose and formation of aldehyde which react with primary amino group to cause color change.
- Peroxide residues in povidone responsible for the enhanced formation of the N-oxide degradation product of the oestrogen receptor modulator, Raloxifene.

# 3. BIOPHARMACEUTICAL INTERACTION

- These are the interactions which are observed **after administration of medicine**. These interactions occur in the form of-

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- ✓ The interaction is between the medicine (drug substance and excipients) and the body fluids
- ✓ The interactions have the tendency to influence the rate of absorption of the drug.

Various eg. of these interactions are as follows-

**a) Premature breakdown of enteric coat –**

Enteric coating polymers e.g., **cellulose acetate phthalate and hydroxyl propyl cellulose acetate phthalate**,

dissolve prematurely in the stomach in the presence of antacids or drugs

cause increase in the pH of the stomach

Cause premature release of API in stomach itself, which results in degradation of drug in stomach.

e.g., side effects like gastric bleeding as in the case of NSAIDs.

**b) Increase in gastrointestinal motility-**

Many excipients such as **sorbitol** and **xylitol** have the tendency to increase gastrointestinal motility, thus reducing the available time for absorption of drugs like **Metoprolol.**

**c) Effect on P-glycoprotein efflux transporter-**

P**-glycoprotein** interferes in the bioavailability of different anticancer and other drug substances. Thus, several excipients e.g., Span 20, Tween 20, Tween 80, Pluronic, Poloxamer etc. are incorporated in the formulations which help in inhibition of P**-glycoprotein** to enhance availability of the drug into the cell, to produce the desired action.

# THANK YOU