# Excipients

- **Excipients** facilitate formulation design to perform a wide range of functions to obtain the desired properties for the finished drug product.
- Historically, pharmaceutical excipients have been regarded as inert additives, but this is no longer the case.
- Each additive must have a clear justification for inclusion in the formulation and must perform a defined function in the presence of the active and any other excipients included in the formulation.
- Excipients may function, for example, as an

**antimicrobial preservative** | **solubility enhancer** | **stability enhancer** | **taste masker**





Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882



THE UNIVERSITY OF JORDAN

# Excipients

- **Excipients** are selected based on their

Chemical / Physical compatibility with drugs | Regulatory acceptance | Processability

- Excipients impact the properties of a powder mixture, such as flowability, density, compactibility, and adhesiveness.
- For example, different **fillers** are selected carefully to balance the ***plasticity***, ***elasticity***, and ***brittleness*** of the pre-compaction powder mixture, in order to make large-scale production feasible.

Topic 2 - Design of Solid Dosage Formulations



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

# Excipients

- For tablets, excipients are needed both for the facilitation of the tableting process (e.g. *glidants*) and for the formulation (e.g. *disintegrants*).
- Except for *diluents*, which may be present in large quantity, the level of excipient use is usually limited to only a **few percent** and some lubricants are required at **less than 1%**.



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

# Types & Functions of Excipients for Tablet Production

| Excipient | Function | Some Examples of Excipients |
|---|---|---|
| **Diluents** | Act as bulking/filling material | Sugars, lactose, mannitol, sorbitol, sucrose, calcium salts, microcrystalline celluloses |
| **Binders and adhesives** | Holds powder together | Sugars, glucose, polymers, starch, gelatin |
| **Disintegrants** | To facilitate the breakup of the tablet in the gastrointestinal tract | Croscarmellose sodium (CCS), sodium starch glycolate (SSG), crospovidone |
| **Glidants** | Improve the flow of granules, needed for compression | Silica, magnesium stearate (MgSt), talc |

Topic 2 - Design of Solid Dosage Formulations


Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

# Types & Functions of Excipients for Tablet Production

| Excipient | Function | Some Examples of Excipients |
|---|---|---|
| **Lubricants** | Reduces friction between granules and the compression equipment | MgSt, stearic acid, talc, sodium lauryl sulfate (SLS) |
| **Antiadherents** | To minimize the problems if sticking to the tablet punch head | Talc, cornstarch, SLS, MgSt |
| **Colorants** | For identification and marketing | Natural pigments and synthetic dyes |
| **Flavors and sweeteners** | To improve the taste of chewable tablets | Mannitol, aspartame |



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

# Excipients

- Some of the tableting excipients may exert effects in opposition to each other.

*Binders & Lubricants*
- bonding and waterproofing properties

*Disintegrants*
- disintegration action

- In addition, some of these tableting excipients may possess **more than one function** that may be **similar** (e.g. talc as *lubricant* and *glidant*) or **opposite** (e.g. starch as *binder* and *disintegrant*) to each other.

Topic 2 - Design of Solid Dosage Formulations


Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

# Excipients

- The sequence of adding the excipients during tablet production depends on the function of the excipient.
  - *Diluents* and *binders* are to be **mixed with the active ingredient early** on for making granules
  - *Disintegrants* may be added **before granulation** (i.e. inside the granules), and/or **during the lubrication step** (i.e. outside the granules) **before tablet compression**.





Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

# Drug–Excipient Compatibility Study

Topic 2 - Design of Solid Dosage Formulations



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882

Dr. Linda Al-Hmoud

# Drug–Excipient Compatibility Study

- Excipient compatibility testing provides a preliminary evaluation of the physical and chemical interactions that can occur.
- Testing is carried under stressed temperature and humidity conditions, between a drug and potential excipients.
- This helps excipient selection, particularly for tablet formulations in order to minimize unexpected formulation stability problems during product development.
- Traditionally, a binary mixture of drug with the excipient being investigated is intimately mixed, and the ratio of drug to excipient is often 1 : 1; however, other mixtures may also be investigated.
  - These blends were stored at various temperatures and humidity, and analyzed for potential degradation products.



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

THE UNIVERSITY OF JORDAN

# Drug–Excipient Compatibility Study

- More recently, the use of a model formulation approach to excipient screening has become much more widespread across the industry.
  - Model formulations include commonly used excipients in each functional category such as fillers, binders, disintegrants, and lubricants, and those with different chemical structures viz. celluloses, starches, and sugars.
  - Both wet and dry model formulations may be prepared for stability testing.
  - It is recommended that a Design of Experiment (DOE) be used to assist in the development and interpretation of results for these types of studies.



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

# Typical Excipients Selected for a Model Formulation Study

| Excipient Type | % Composition | Level 1 | Level 2 |
|---|---|---|---|
| API | 10 | — | — |
| Filler 1 | 38–40 | MCC | Mannitol |
| Filler 2 | 38–40 | Dicalcium phosphate | Spray-dried lactose |
| Surfactant | 0–4 | None | Sodium lauryl sulfate |
| Binder | 4 | PVP | HPC |
| Disintegrant | 5 | Sodium starch glycolate | Croscarmellose sodium |
| Lubricant | 1 | Magnesium stearate | Sodium stearyl fumarate |
| Wet granulation | 20% (w/w) water | No | Yes |



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud



# Drug–Excipient Compatibility Study

- Powders are physically mixed and may be granulated or compacted to accelerate any possible interaction.
- Samples may be exposed in open pans or sealed in bottles/vials to mimic product packaging.
- The storage conditions used vary widely in terms of temperature and humidity, but a temperature of 40 °C for storage of compatibility samples is considered appropriate.
- Some compounds may require higher temperatures to make reactions proceed at a rate that is measured over a convenient time period.
- Methods of analysis also vary widely, ranging from thermal techniques (DSC) to chromatographic techniques (TLC and HPLC) to microcalorimetry.



Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

## Formulation Composition for Excipient Compatibility Study utilizing partial factorial design

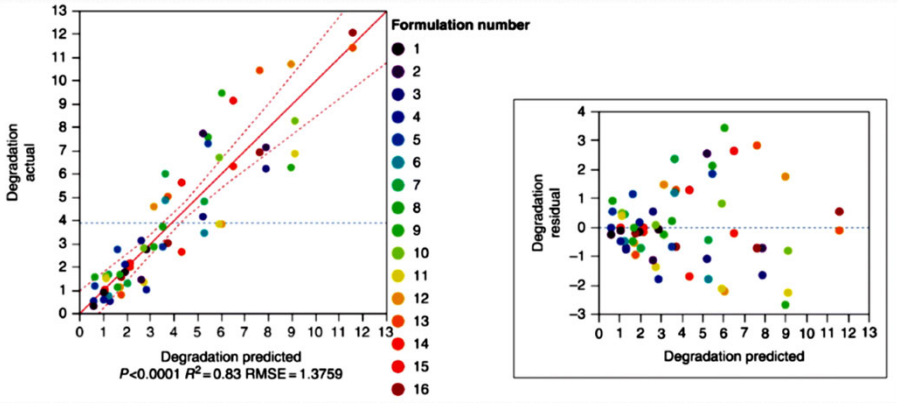
| Formulation Composition and Numbers | 10% | 38–40% | 38–40% | 0–4% | 4% | 1% | 5% | 20% (w/w) Water |
|---|---|---|---|---|---|---|---|---|
| 1 | API | MCC | ATab | None | PVP | MgSt | SSG | Dry (no) |
| 2 | API | MCC | ATab | None | HPC | MgSt | CCS | Wet |
| 3 | API | MCC | ATab | SLS | PVP | SSF | CCS | Wet |
| 4 | API | MCC | ATab | SLS | HPC | SSF | SSG | Dry (no) |
| 5 | API | MCC | Lactose | None | PVP | SSF | CCS | Dry (no) |
| 6 | API | MCC | Lactose | None | HPC | SSF | SSG | Wet |
| 7 | API | MCC | Lactose | SLS | PVP | MgSt | SSG | Wet |
| 8 | API | MCC | Lactose | SLS | HPC | MgSt | CCS | Dry (no) |
| 9 | API | Mannitol | ATab | None | PVP | SSF | SSG | Wet |
| 10 | API | Mannitol | ATab | None | HPC | SSF | CCS | Dry (no) |
| 11 | API | Mannitol | ATab | SLS | PVP | MgSt | CCS | Dry (no) |
| 12 | API | Mannitol | ATab | SLS | HPC | MgSt | SSG | Wet |
| 13 | API | Mannitol | Lactose | None | PVP | MgSt | CCS | Wet |
| 14 | API | Mannitol | Lactose | None | HPC | MgSt | SSG | Dry (no) |
| 15 | API | Mannitol | Lactose | SLS | PVP | SSF | SSG | Dry (no) |
| 16 | API | Mannitol | Lactose | SLS | HPC | SSF | CCS | Wet |





# Drug–Excipient Compatibility Study

- Regression model defined for assessing the effect of formulation and time on degradation growth at a storage condition of 40 °C / 75% RH.

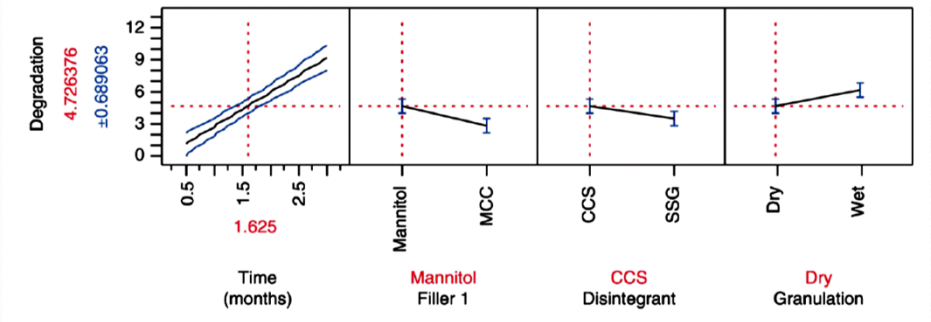





Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882
Dr. Linda Al-Hmoud

# Drug–Excipient Compatibility Study

- Filler 2, Surfactant, Binder, and Lubricant did not show significance
- **Prediction profiler**




- Within Filler 1 mannitol causes more degradation as compared to MCC.
- SSG is better than CCS among disintegrant.
- Dry blend is better than wet granulation as the latter causes more degradation.

Chemical Engineering Department | University of Jordan | Amman 11942, Jordan
Tel. +962 6 535 5000 | 22882



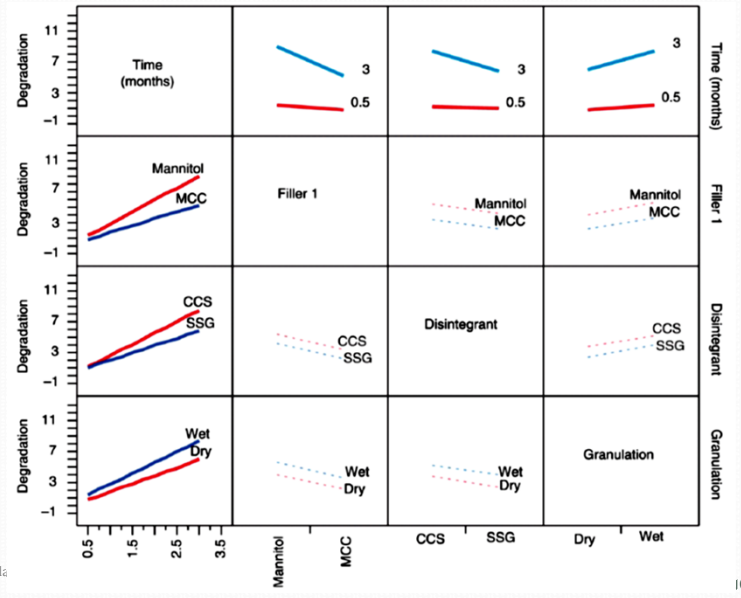






# Drug–Excipient Compatibility Study

- **Interaction profiles**
  - Both mannitol and CCS could be detrimental for the stability of the API and are not being assessed for formulation development.
  - Wet granulation is to be avoided to increase the shelf life.




Chemical Engineering Department | University of Jorda
Tel. +962 6 535 5000 | 22882