seminar on
CRYSTAL GROWTH AND ITS PREVENTION

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INTRODUCTION

• **CRYSTAL**: A crystal is a three dimensional arrangement of atoms and crystalline solid refers to aggregates of atoms/molecules/their ions arranged in a regular repetition.

• **Crystallization** is a process of formation of crystals from the solvent in which the solute is dissolved.

• Crystallization is employed as the final step in the purification of a solid.
A crystalline particle is characterized by definite internal and external structures.

**Crystal habit:** Describes the external shape of a crystal.

**Polymorphic state** refers to the definite arrangement of the molecules inside the crystal lattice.

**Different crystal habits:**
- Acicular
- Aggregate
- Blade
- Dendritic
- Cubic
- Fiber
- Prismatic

Various indices of dosage form performance such as particle orientation, flowability, packing, compaction, suspension stability and dissolution can be altered with changes in crystal habit.
OBJECTIVE

The knowledge and concept of crystal growth forms the basis for understanding the formation of crystals and various factors influencing the crystal growth.

The crystal growth studies help in

• Improving the physical stability of pharmaceutical formulations.
• Maintaining uniformity in raw material characteristics.
• Maintaining uniformity in batch to batch dosage form performance.
Process of crystal growth:

It involves three steps:

1. Supersaturation
2. Nucleation
3. Growth of nuclei into crystals

**Supersaturation**: When the solubility of a compound in a solvent exceed the saturation solubility, the solution becomes supersaturated and the compound may crystallize.

It is the basic driving force for crystallization.

**Methods for supersaturation:**

- By increasing solute concentration
- By decreasing solute solubility
**Nucleation:** Nucleation refers to the birth of very small bodies of a new phase within a homogenous supersaturated liquid phase.

The initially formed solid particles are of molecular size which are termed as nuclei.
Growth of nuclei into crystal

As stable nuclei form, they grow into macroscopic crystals. This portion of the crystallization process is known as “crystal growth”. This process consists of several stages through which the growth units pass.

These include the following:

- **Transport of the growth unit** from or through the bulk solution to an impingement site, which is not necessarily the final growth site.
- **Adsorption** of the growth unit at the impingement site.
- **Diffusion** of the growth units from the site of impingement to a growth site.
- **Incorporation** into the lattice.
Process variables of crystallization & their influence on dosage form performance

- Supersaturation
- Rate of cooling
- Degree of solution agitation
- Temperature
- Nature of crystallizing solvent
- Presence of impurities
Crystal Growth in Disperse Systems

Ostwald Ripening:

The growth of large particles at the expense of smaller ones, because of a difference in solubility rates of different size particles.
This effect can be expressed by the following relationship

\[ \log \frac{S}{S_0} = \frac{k}{2.303 \cdot r} \]

- Where \( S \) is the initial solubility of small particles
  - \( S_0 \) is the solubility rate of large particles at equilibrium
  - \( r \) is the particle radius in cm
  - \( k \) is a constant that includes surface tension, temperature, molar volume and thermodynamic terms (\( k=1.21 \times 10^{-6} \))

For example, the solubility rate of a 0.2-\( \mu \)m particle, is 13%. For a 2-\( \mu \)m particle, it is 1%, and for particles above 20 \( \mu \)m, it is negligible.
Factors Affecting Crystal Growth in Drug Formulations

- Particle size distribution
- Dissolution and Recrystallization
- Changes in pH
- Temperature fluctuations
- Polymorphic transformations
Particle size distribution

- Particle size distribution of dispersed system increases during aging which ultimately results in the crystal growth.
- Drug particle size is the important factor influencing product appearance, stability of pharmaceutical suspensions and the therapeutic effect of active ingredients.

Dissolution and recrystallization

- Particle size, temperature and polymorphic transformations influence the solubility and hence the dissolution of a drug and may cause recrystallization.
Changes in pH

- The solubility of weakly acidic or basic drugs is influenced by pH.

- The changes in pH produces degree of supersaturation which gives rise to nucleation and crystal growth.

- Drug decomposition may occur because the product of decomposition causes a shift in the pH which in turn have a marked effect on solubility.
Temperature fluctuations:

Crystal growth due to temperature fluctuations during storage is of importance especially when the suspensions are subjected to temperature cycling of 20ºC or more.

These effects depend on the magnitude of temperature change, the time interval and the effect of temperature on the drug’s solubility and subsequent recrystallization process.

Changes in temperature may change particle size distribution and polymorphic form of drug. Thus resulting in the crystal growth and it also alters the absorption rate and bioavailability.
Polymorphic transformations:

- Drugs may undergo a change from one metastable polymorphic form to a more stable polymorphic form.
- This leads to the formation of distinct new crystalline entities during storage is possible.
- For Ex: An originally anhydrous drug in a suspension may rapidly or slowly form a hydrate. These various forms may exhibit different solubilities, melting points.
Need For Crystal Growth Prevention in Drug Formulations

- **Suspensions and Solutions** -- physical stability
- **Parenterals** -- syringeability and injectability
- **Aerosols** -- valve clogging and inaccuracy of dose
- **Ophthalmic** -- ocular irritation
- **Tablets** -- prolonged disintegration, cracks, altered appearance and altered bioavailability
Crystal Growth Inhibitors

Surfactants: By Adsorption process

Anionic - Sodium lauryl sulfate, sodium dodecyl sulfate, sodium dodecyl benzene sulphonates.

Cationic – Quaternary ammonium compounds like CTAB, TDAC, Benzylkonium chloride, Benzathonium chloride.

Nonionics: Tweens, Spans, Carbowaxes (High molecular weight PEGs) Pluronics.

Polymers: By forming a net like film

PVP, PEGs, Poly alcohol, Poly ethylene oxide, Bovine serum albumin

Protective colloids: By creation of protective coat or boundary layer
Prevention Of Crystal Growth

- Selection of particles with a **narrow range of particle sizes**, such as micro crystals between 1 to 10 μ.

- Selection of a stable crystalline drug form that usually exhibits **lower aqueous solubility**. The crystalline form that is physically most stable usually has the highest melting point.

- High-energy milling should not be used during particle size reduction.

- Micro crystals are best formed by **controlled precipitation** techniques or shock cooling.
A water-dispersible surfactant or wetting agent dissipates the free surface energy of particles by reducing the interfacial tension between the solid and the suspending vehicle.

A protective colloid, such as gelatin, gum, or a cellulosic derivative, is used to form a film barrier around the particles, inhibiting dissolution and subsequent crystal growth.

The viscosity of the suspending vehicle is increased to retard particle dissolution and subsequent crystal growth.
Temperature extremes during product storage (freeze–thaw conditioning) must not occur.

Supersaturation favours the formation of needle-like crystals and should be avoided.

Rapid or shock cooling and high agitation favour the formation of thin, small crystals and should be avoided. Slow crystallization by evaporation yield compact crystals.

Experimentation with different crystallizing solvents is recommended to change crystal size and shape.
- Impurities and foreign substances during crystallization affect the reproducibility and aggregation potential of many drug particle systems.

- Constant crystallizing conditions are essential. Batch-to-batch variation in crystal size and shape is often associated with poor control of processing and crystallization procedures.
CONCLUSION

The knowledge and concept of crystal growth naturally forms the basis for understanding how the crystals form and various factors which influence the crystal growth. Such an understanding of crystal growth studies widely used to describe how to improve physical stability of pharmaceutical formulations.
REFERENCES


Ostwald, W. Studien Uber Die Bildung und Umwandlung Fester Korper Z. Phys. Chem. 1897, 22, 289
THANK YOU!