# How solubility issue develops pharmaceutical products?

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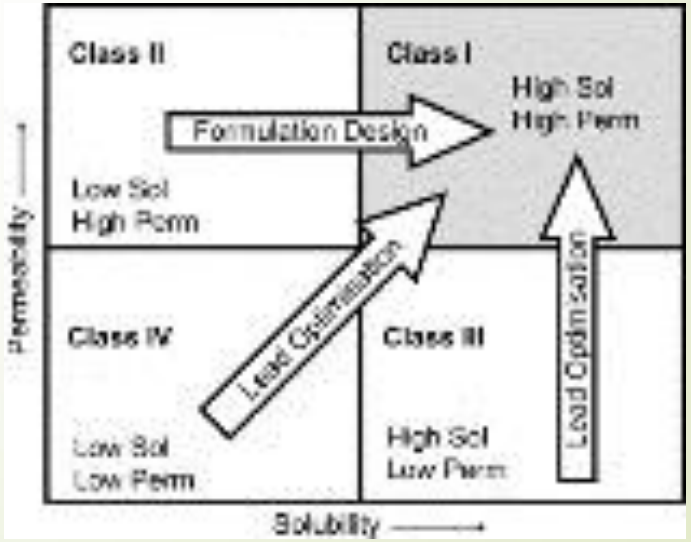
Product development

- Solubility in different solvents is an intrinsic material characteristic for a defined molecule. The aqueous solubility is a major indicator for the solubility in the intestinal fluids and its potential contribution to bioavailability issues.
- Besides the aqueous solubility of a drug substance, its permeability is a second critical aspect for oral bioavailability.

# Biopharmaceutical Classification System (BCS)

- The Biopharmaceutical Classification System (BCS) was introduced in the mid-1990s to classify the drug substances with respect to their aqueous solubility and membrane permeability. Especially for class 2 substances, solubility enhancement is part of the strategies to improve the oral bioavailability.



# Solubility vs dissolution

- Solubility is an **intrinsic** material property that can only be influenced by chemical modification of the molecule as such, like salt complex or prodrug formation.
- In contrast to this, dissolution is an **extrinsic** material property that can be influenced by various chemical, physical or crystallographic means like complexation, particle size, surface properties, solid state modification or solubilization enhancing formulation strategies.

- Solubility is one of the key physicochemical parameters of a new molecule that needs to be assessed and understood very early on in drug discovery and drug candidate selection process. Starting with the first amount of the substance synthesized, commonly a few milligrams, the first series of analytical tests include that of the equilibrium solubility of the substance in a given solvent, as well as the apparent or dynamic solubility, which reflects the concentration of the substance in solution **under certain conditions**. The value of equilibrium solubility is often limited by the test duration, which is normally between 4 and 24 h.

- The enhancement of oral bioavailability of poorly water soluble drugs remains one of the most challenging aspects of drug development. Although salt formation, solubilization, and particle size reduction have commonly been used to increase dissolution rate and thereby oral absorption and bioavailability of such drugs.

# Factors affecting solubility

- Composition of the aqueous media
- Temperature
- pH
- Solid state (amorphous, crystalline)
- Polymorph type
- Counter ions (salt formation)
- Ionic strength

# Strategies

- The solubility or dissolution of the drug substance can be mainly altered on two levels, through **material engineering** of the drug substance or through **formulation approaches**. Whatever route is taken to enhance or modify the solubility and/or dissolution of a lead substance, it needs to be scalable to a commercially viable process later on in the development.

# Characterisation

- In parallel to the analytical characterization of the initial material of the drug substance, substantial efforts are invested into understanding and optimization of the crystalline structure and to identify a potential pseudo-thermodynamic stable form of the substance. These investigations are looking into the polymorphs, solvates and salts formed by the substance under various conditions to identify the most suitable material for dosage form development, scaling up and later manufacturing.

# Analytical Methods

- Therefore different analytical methods have been developed to assess the substance in solution or solid state (precipitates). Analytical methods for the substance in pH-controlled solutions are LC coupled with UV and MS. For the solid state analysis, powder X-ray diffraction, energy dispersive X-ray (EDX), Raman spectroscopy, IR, microscopy (polarized light microscopy (PLM), environmental scanning electron microscopy (ESEM)) and thermal analysis are used.

- Polymorphs appear in a number of different structures as non-mixed polymorphs (free base or acid) or as mixed polymorphs like salts, co-crystals, guest substances, hydrates or solvates. While the polymorph screening focused more on the number of different polymorphs by crystallization in different solvents in the past, it now has shifted towards qualitative data on polymorph formation under thermodynamically controlled conditions to get more accurate data on the potential risk for polymorphic changes in the final dosage form under the expected storage conditions. These constant and controlled conditions include pressure, temperature, solvent and time. Once a polymorph is found and characterized, additional polymorph evaluation experiments should be performed to provide information on its kinetic stability.

# Evaluation

- The evaluation starts with determining, e.g. if the substance forms only one anhydrate or several anhydrates.
- Once different polymorphs have been identified it is important to characterize whether they are monotropically or enantiotropically related. In case of an enantiotropic phase transition, the transition temperature as well as the temperature stability range must be very well characterized.
- Long-term stability is tested in slurry experiments for at least 2 months in different non-solvate forming solvents and/or at temperatures in the stability range of the anhydrates. From this series of polymorph experiments the most thermodynamically stable

# Manufacturing of poorly water soluble

- To improve physicochemical properties of the drug substance with regard to manufacturing, isolation and long-term storage, as well as to improve solubility and/or dissolution properties of the drug substance, **salt formation** is traditionally preferred by medicinal chemists for weak bases or weak acids. Since only **20–30%** of the new molecules form salts easily, the **70–80%** remain challenging (Serajuddin and Pudipeddi, 2002).

# Major formulation strategies for poorly soluble substances

- Particle size reduction
- Solid state engineering
- Solid dispersions
- Microemulsions
- Liposomes
- Complexation (e.g. cyclodextrins)
- Lyophilization
- Co-solvent systems
- Micellar/surfactant systems

Stegemann, Sven, et al. "When poor solubility becomes an issue: from early stage to proof of concept." *European journal of pharmaceutical sciences* 31.5 (2007): 249-261.

# Selection of the best method

- For **ionisable drugs** (anionic, cationic and zwitterionic) **salt formation** is the simplest, most cost-effective strategy to address poor aqueous solubility and enhance bioavailability.
- For **non-ionisable drugs**, or compounds with pKa values in a range where possible salt formation is very limited, **cocrystal** formation is an attractive alternative.
- The only difference between a salt and a cocrystal (composed of a base and an acid), is whether the proton is located on the acid or the base.

- Unlike polymorphs, which generally speaking contain only the API  within the crystal lattice, cocrystals are composed of an API with a neutral guest compound conformer in the crystal lattice. Similarly, unlike salts, where the components in the crystal lattice are in an ionized state, a cocrystal's components are in a neutral state and interact via non-ionic interactions,

Elder, David P., René Holm, and Heidi Lopez de Diego. "Use of pharmaceutical salts and cocrystals to address the issue of poor solubility." *International journal of pharmaceutics* 453.1 (2013): 88-100.

# Challenges

- When salts can be prepared, an increased dissolution rate in the gastrointestinal tract may not be achieved in many cases because of the reconversion of salts into aggregates of their respective acid or base forms. The solubilization of drugs in organic solvents or in aqueous media by the use of surfactants and cosolvents leads to liquid formulations that are usually undesirable from the viewpoints of patient acceptability and commercialization.
- Although particle size reduction is commonly used to increase dissolution rate, there is a practical limit to how much size reduction can be achieved by such commonly used methods as controlled crystallization, grinding, etc. The use of very fine powders in a dosage form may also be problematic because of handling difficulties and poor wettability

# Early promise

- In 1961, Sekiguchi and Obi developed a practical method whereby many of the limitations with the bioavailability enhancement of poorly water-soluble drugs just mentioned can be overcome. This method, which was later termed solid dispersion, involved the formation of eutectic mixtures of drugs with water-soluble carriers by the melting of their physical mixtures. Sekiguchi and Obi suggested that the drug was present in a eutectic mixture in a microcrystalline state.

- Later, Goldberg et al. demonstrated that all the drug in a solid dispersion might not necessarily be present in a microcrystalline state; a certain fraction of the drug might be molecularly dispersed in the matrix, thereby forming a solid solution. In either case, once the solid dispersion was exposed to aqueous media and the carrier dissolved, the drug was released as very fine, colloidal particles. Because of greatly enhanced surface area obtained in this way, the dissolution rate and the bioavailability of poorly water-soluble drugs were expected to be high.

Serajuddin, Abu TM. "Solid dispersion of poorly water-soluble drugs: Early promises, subsequent problems, and recent breakthroughs." *Journal of pharmaceutical sciences* 88.10 (1999): 1058-1066.

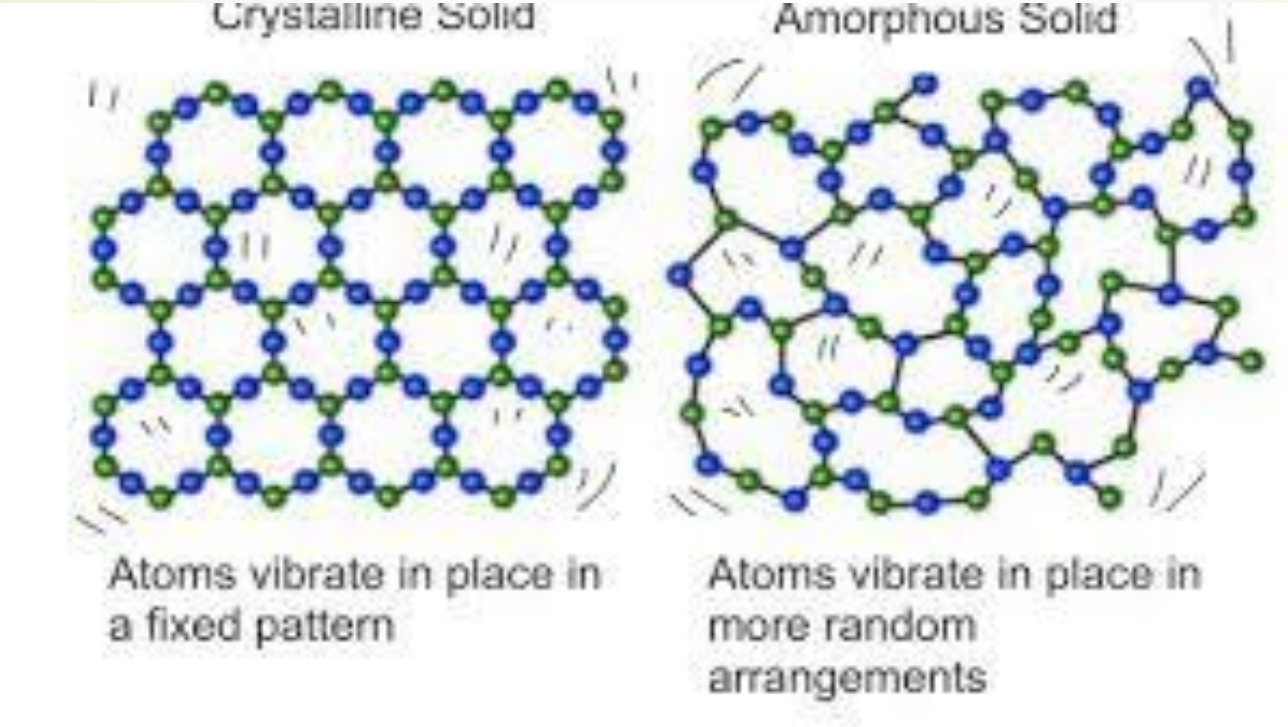
# Amorphisation

- The amorphous state is characterized by the absence of the long-range, three-dimensional molecular order characteristic of the crystalline state.
- From a practical standpoint, an amorphous material can be obtained in two ways:

1. (i) by cooling the molten liquid until the molecular mobility is ‘‘frozen in,’’ thus producing the glass.
2. (ii) by gradually inducing defects in the crystal until the amorphous form is attained.

- In each of the two situations described above, X-ray powder diffraction (PXRD) analysis would result in characteristically amorphous patterns that are essentially undistinguishable.

# Amorphous Vs Crystalline



# The thermodynamic route

In this case equilibrium phase transformation from the liquid to the solid state, where the molecules are randomly distributed. The material is quenched so that the thermal motions of molecules are drastically slowed down to a time scale larger than that of structural relaxation. As a consequence, all the molecules are instantly frozen in a nonequilibrium state, which is generally referred to as glassy (term typically used for inorganic compounds and metals) or amorphous (term typically used for organic compounds) state.

# The kinetic route

- The crystalline state away from equilibrium by progressively disturbing its crystal structure, thus increasing its free energy. This nonequilibrium state can still be considered crystalline in a broad sense.
- This type of higher energy crystal is commonly referred to as defective crystal, defect crystal or defected crystal in the literature. In principle, if crystal defects accumulate to certain critical level, a defective crystal could eventually transform into an amorphous phase if the kinetics is favourable.

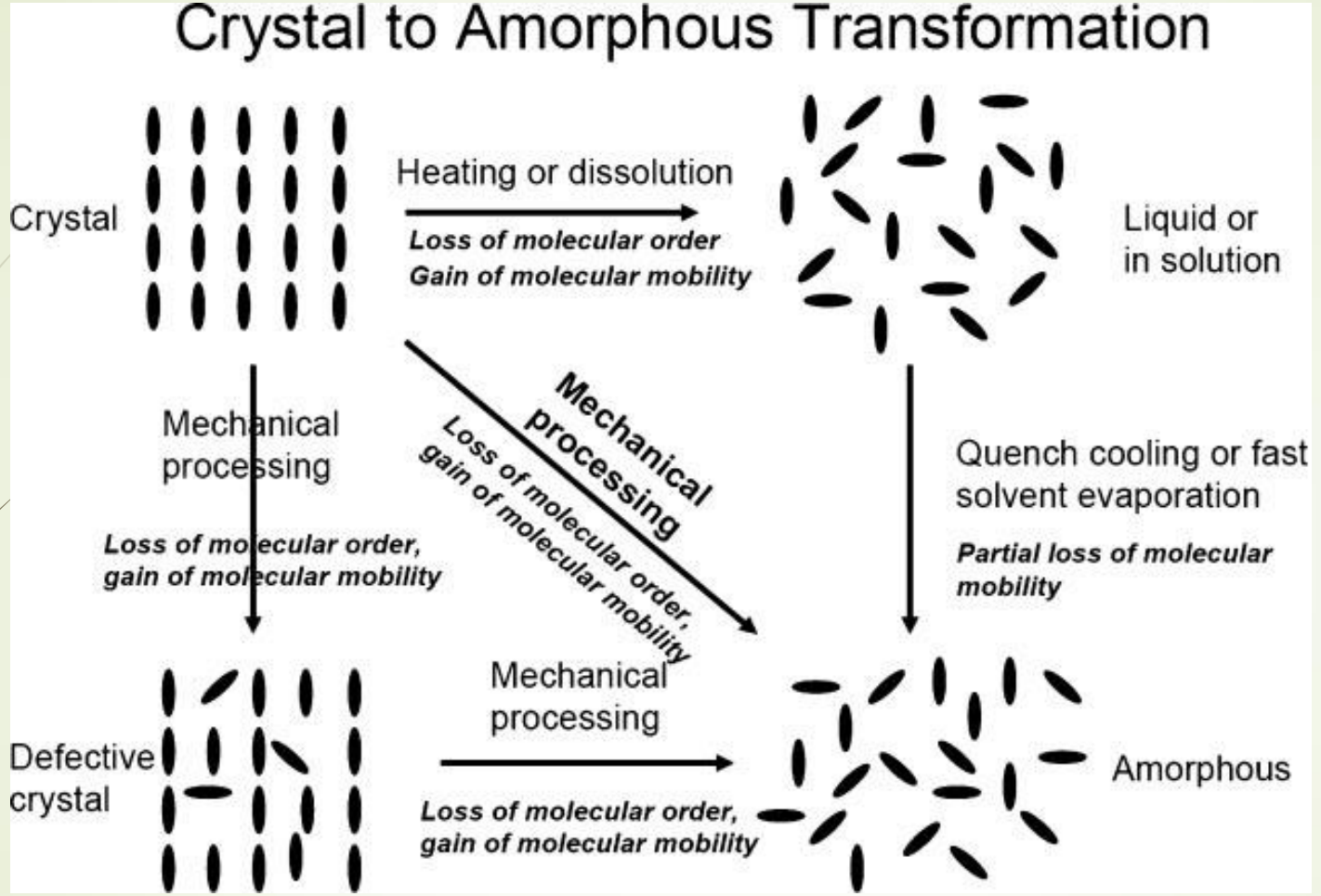



Figure 1. Schematic representation of two pathways to create the amorphous phase from the crystal during pharmaceutical processing.

- The thermodynamic route has been extensively used to prepare amorphous pharmaceutical products by processes such as quench melt, freeze drying, spray drying, etc. These processes are normally considered as means of vitrification, that is, **intentional** production of the amorphous form of the material of interest. The kinetic route is typically associated with **unintentional** amorphization in drug products. Common manufacturing process such as milling, compression, granulation or drying induce amorphization in pharmaceutical materials.

- In the free energy scale, the stable crystal and amorphous form occupy the lowest and highest level, respectively, with the defective crystal somewhere in between although closer to the crystal. In this framework, the gradual accumulation of defects described above would correspond to a higher free energy level until the amorphous form is attained.
- It is generally believed that when milling under ambient conditions, the intense mechanical energy involved can lead to local heating and cause small crystalline regions to melt and quench into the amorphous form. In other words, local heating could lead to vitrification during processing in many cases.

Feng, Tao, Rodolfo Pinal, and M. Teresa Carvajal. "Process induced disorder in crystalline materials: differentiating defective crystals from the amorphous form of griseofulvin." *Journal of pharmaceutical sciences* 97.8 (2008): 3207-3221.