

Review Article

Crystal Engineering an Approach for Solubility Enhancement of Poorly Water Soluble Drugs

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ABSTRACT

Major limitation for product development of multiple drugs is the poor aqueous solubility. Crystal engineering is the best mechanism to improve the solubility. Cocrystallization is bicomponent system in which bond formation takes place between drug and coformer which improve the solubility and flow properties of poorly water soluble drugs. Cocrystallization does not interfere with chemical properties and biological activity of drug. Improvement of flow and compressibility is an additional advantage of implementing cocrystallization for solubility improvement.

Keywords: Cocrystal, cocrystallization, solubility, dissolution

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Conflict of Interest: None Declared!

(Received 15 May 2019; Accepted 30 May 2019; Published 24 July 2019) ISSN: 2347-8136 ©2018 JMPI

INTRODUCTION:

Absorption of the drug is limited mostly by dissolution and permeability. Dissolution of drug is mostly depends on its aqueous solubility of drug. BCS class II and class IV drug are the drugs with solubility limitations. Development of dosage form become challenging for drugs with poor aqueous solubility. Solubility enhancement is having enough scope during formulation development of poorly water soluble drugs. Use of coformers makes cocrystallization significantly different from other polymorphic forms, hydrates and solvates. Supramolecular synthone formation is the key mechanism behind cocrystal formation. Cocrystallization basically requires formation of proper hydrogen bonding for solubility enhancement. Supramolecular synthons are spatial arrangements of intermolecular interactions in which homo and heterosynthone important for structural aspects of hydrogen bonding.

Different chemical compounds have been used as cocrystal formers in which solid carboxylic acids was found to be more preferred due to its significant hydrogen bond formation ability which important structurally for the formation of cocrystals.¹

Design and Development of Cocrystals

Bicomponent system of cocrystal is consisting of API (Active Pharmaceutical Ingredient) and CCF (Cocrystal Formers) in particular stoichiometric ratio. From previous literature studies it can be easily observe that 1:1 ratio of API and CCF was found to be better with the aim solubility enhancement. Different techniques of cocrystal formation are used to form with the formerly decided stoichiometric ratio of API and CCF. After preparation of cocrystals the in-vitro characterization and screening is important to interpret the objectives of cocrystallization. Formulation development and evaluation with cocrystal is important to prove comparative advantage of cocrystallization.²

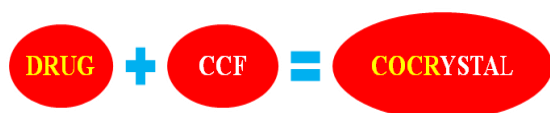


Figure 1: Cocrystal formation

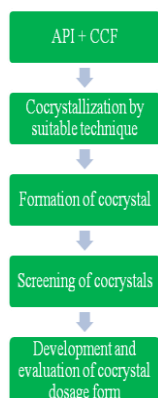


Figure 2: Flow chart for process of cocrystal formulation development.

Techniques of Cocrystallization ³

Cocrystallization can be achieved by different solid bases and solvent based techniques with good efficiency. The selection of technique is mostly depends compatibility of drug and cocrystal with the technique and subsequent results targeted.

| Technique of Cocrystallization | Description |
|------------------------------------|---|
| a) Neat grinding | In this technique drug and cocrystals are grinded together for fixed period of time. At lab neat grinding can be the method to achieve the cocrystallization. |
| b) Liquid assisted grinding | Drug and cofomer are grinded with drop wise addition of liquid medium to improve the efficiency of cocrystallization. The selection of solvent is based on its safety and efficacy. |
| c) Extrusion | Hot melt extrusion technique is used for cocrystallization which involves application of high shear rate which leads to formation of agglomerates. |
| d) Cooling cocrystallization | Cocrystallization takes place between drug and cofomer with the mechanism of cooling. This is one major solvent based technique used for cocrystallization. |
| e) Evaporative cocrystallization | Evaporation of solvent from both drug and conformers is the basic mechanism behind crystallization. |
| f) Reaction cocrystallization | Cocrystallization is takes place precipitation |
| g) Super critical fluid technology | Use of supercritical fluid for cocrystallization. |

Table 1: Techniques of cocrystal preparation.

SCREENING OF COCRYSTALS ⁴⁻⁶

Cocrystals are screened for its physicochemical characterization. Different analytical techniques are carried out. Physical characterization, solubility determination is important for screening of cocrystals.

1) Solubility determination

Enhancement in solubility is major aim of crystal engineering so comparative solubility of Active Pharmaceutical Ingredient and Cocrystal is important.

2) Differential Scanning Colorimetry (DSC)

Melting point of pure drug and cocrystal is an indicative tool for determination of newly formed crystalline structure so DSC is important tool for screening of cocrystals. Formation of cocrystal ultimately causes changes in melting point.

3) Infra Red (IR) and Raman Spectroscopy

Infrared spectroscopy and Raman spectra are important for interpretation of structural components of API and cocrystals. Different

functional groups present in drug and cocrystal are determined by IR and Raman spectroscopy.

4) X-Ray Diffraction (XRD) Study

Crystalline structures have the better determination with powder X-ray diffraction technique so it is important part in the screening of cocrystals. The sharp peaks in XRD graph indicate crystalline structure.

5) Scanning Electron Microscopy (SEM)

SEM can be the optional technique to interpret cocrystals. In SEM crystal lattice observed distinguishes between drug and co crystal.

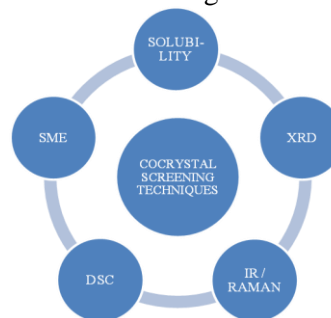


Figure 3: Screening techniques of cocrystal

Application of Cocrystallization⁷

- 1) Cocrystallization improves the micromeritic properties of Active Pharmaceutical Ingredient (API).
- 2) Improvement in solubility, dissolution and bioavailability.
- 3) Improvement in physical and chemical stability.

CONFLICT OF INTEREST

No conflict of interest

CONCLUSION

Multicomponent technique of cocrystallization is efficient in solubility enhancement for poorly water soluble drugs. Increase in solubility by crystal engineering increase increases dissolution and ultimately increases bioavailability. Improvement of micromeritic and flow property creates better scope for product development. Cocrystallization does not affect the biological activity of drug and also provide long term stability

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