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A REVIEW ON PHARMACEUTICAL COCRYSTALS

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ABSTRACT

Pharmaceutical cocrystals have emerged as an effective crystal engineering strategy to improve the physicochemical and biopharmaceutical properties of active pharmaceutical ingredients (APIs). A cocrystal is a multicomponent crystalline system composed of an API and a pharmaceutically acceptable coformer held together through non-covalent interactions such as hydrogen bonding, π-π stacking, and van der Waals forces. Cocrystallization has gained significant attention because it can improve solubility, dissolution rate, stability, bioavailability, compressibility, and mechanical properties without altering the pharmacological activity of the drug. Various methods including solvent evaporation, grinding, slurry conversion, hot melt extrusion, and supercritical fluid technology are used for cocrystal preparation. The present review discusses the concept, classification, advantages, disadvantages, preparation methods, characterization techniques, evaluation parameters, and pharmaceutical applications of cocrystals.

KEYWORDS: Cocrystals, Crystal Engineering, Solubility Enhancement, Coformer, Pharmaceutical Technology, Bioavailability.

INTRODUCTION

Approximately 40–70% of newly discovered drug molecules exhibit poor aqueous solubility, resulting in limited oral bioavailability and therapeutic effectiveness.[1,2] Various approaches such as salt formation, solid dispersions, particle size reduction, complexation, and lipid-based formulations have been employed to overcome solubility limitations.[3,4] Pharmaceutical cocrystals represent an advanced crystal engineering approach for modifying the physicochemical properties of drugs while maintaining their pharmacological activity.[5,6] A pharmaceutical cocrystal consists of an API and one or more neutral coformers in a definite stoichiometric ratio within the same crystal lattice.[7] The concept of pharmaceutical cocrystals has attracted considerable interest because cocrystallization can improve solubility, dissolution rate, stability, hygroscopicity, mechanical behavior, and bioavailability.[8,9] Unlike salts, cocrystals can be developed for both ionizable and non-ionizable drug molecules.[10] The United States Food and Drug Administration (FDA) and European Medicines Agency (EMA) have recognized cocrystals as important pharmaceutical solid forms, encouraging extensive research in this field.[11,12]

Pharmaceutical Cocrystals

Pharmaceutical cocrystals are crystalline materials composed of two or more different molecular entities, generally an API and a coformer, held together by intermolecular interactions in a single crystal lattice.[13]

Types of Cocrystals

1. Drug-Drug Cocrystals

Contain two active pharmaceutical ingredients within the same crystal lattice.[14]

2. Drug-Coformer Cocrystals

Contain an API and a pharmaceutically acceptable coformer such as saccharin, nicotinamide, or caffeine.[15]

3. Ionic Cocrystals

Contain ionic compounds and neutral molecules linked through non-covalent interactions.[16]

4. Binary Cocrystals

Contain one API and one conformer.[17]

5. Ternary Cocrystals

Contain one API and two different coformers.[18]

Advantages of Pharmaceutical Cocrystals

- Improve aqueous solubility.[19]
- Enhance dissolution rate.[19]
- Increase oral bioavailability.[20]
- Improve physical stability.[20]
- Enhance mechanical properties and compressibility.[21]
- Reduce hygroscopicity.[21]
- Improve patient compliance.[22]
- Suitable for non-ionizable drugs.[22]

Disadvantages of Pharmaceutical Cocrystals

- Scale-up challenges during manufacturing.[23]
- Possibility of phase transformation during storage.[23]
- Selection of suitable coformer can be difficult.[24]
- Regulatory complexities.[24]
- Stability issues under extreme environmentalconditions.[25]

Applications of Pharmaceutical Cocrystals

1. Solubility Enhancement

Improves aqueous solubility of poorly soluble drugs.[26]

2. Bioavailability Enhancement

Increases absorption and therapeutic effectiveness.[27]

3. Stability Improvement

Enhances chemical and physical stability.[27]

4. Taste Masking

Improves palatability of bitter drugs.[28]

5. Controlled Drug Delivery

Provides modified drug release profiles.[28]

6. Mechanical Property Enhancement

Improves tabletability and manufacturability.[29]

Formulation Considerations

The development of pharmaceutical cocrystals requires careful selection of API and coformer based on molecular complementarity, hydrogen-bonding capability, thermodynamic stability, and regulatory acceptability.[30]

Common Coformers

Nicotinamide
Saccharin
Urea
Caffeine
Succinic Acid
Citric Acid
Malonic Acid
Glutaric Acid
Oxalic Acid
Benzoic Acid

Methods of Preparation

1. Solvent Evaporation Method

API and coformer are dissolved in a suitable solvent and allowed to evaporate slowly to obtain cocrystals.[31]

2. Grinding Method

The API and coformer are triturated using dry or liquid-assisted grinding.[32]

3. Slurry Conversion Method

Components are suspended in a small quantity of solvent and stirred until cocrystals form.[32]

4. Hot Melt Extrusion

Drug and coformer are mixed and processed under controlled heat and pressure.[33]

5. Supercritical Fluid Technique

Supercritical carbon dioxide is utilized for cocrystal formation.[33]

6. Spray Drying

Solutions containing API and coformer are atomized and dried rapidly.[34]

Evaluation and Characterization

1. Melting Point Determination

Used to confirm cocrystal formation and purity.[35]

2. Differential Scanning Calorimetry (DSC)

Determines thermal behavior and phase transitions.[35]

3. Powder X-Ray Diffraction (PXRD)

Identifies crystalline structure and confirms cocrystal formation.[36]

4. Fourier Transform Infrared Spectroscopy (FTIR)

Evaluates intermolecular interactions and hydrogen bonding.[36]

5. Scanning Electron Microscopy (SEM)

Studies surface morphology and particle characteristics.[37]

6. Solubility Study

Determines solubility enhancement compared to pure drug.[37]

7. Dissolution Study
Evaluates dissolution rate improvement.[38]

8. Stability Study
Assesses physical and chemical stability under storage conditions.[38]

9. Nuclear Magnetic Resonance (NMR)
Confirms molecular interactions within the crystal lattice.[39]

10. Single Crystal X-Ray Diffraction (SCXRD)
Provides detailed crystal structure information.[40]

CONCLUSION

Pharmaceutical cocrystals represent a promising strategy for improving the physicochemical and biopharmaceutical properties of drugs. They offer significant advantages in terms of solubility, dissolution, stability, and bioavailability while preserving the pharmacological activity of the API. Advances in crystal engineering and characterization techniques have expanded the potential applications of cocrystals in pharmaceutical development. Future research should focus on large-scale manufacturing, regulatory acceptance, and commercialization of cocrystal-based drug products.

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