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COCRYSTALS AS A NOVEL STRATEGY TO ENHANCE THE SOLUBILITY AND DISSOLUTION RATE OF ZOLMITRIPTAN: A COMPREHENSIVE REVIEW

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ABSTRACT

Poor aqueous solubility remains one of the major challenges in the development of orally administered drug molecules, particularly those belonging to Biopharmaceutics Classification System (BCS) class II and IV.[1,2] Zolmitriptan, a selective 5-HT1B/1D receptor agonist widely used in the treatment of migraine, exhibits limited aqueous solubility, which may restrict its dissolution rate and onset of therapeutic action.[3,4] Pharmaceutical cocrystallization has emerged as a promising crystal engineering approach to modify the physicochemical properties of active pharmaceutical ingredients (APIs) without altering their pharmacological activity.[5–7] This review critically summarizes the concept of pharmaceutical cocrystals, their classification, design strategies, and preparation methods, with a special focus on the potential of cocrystallization to enhance the solubility and dissolution rate of zolmitriptan. The article discusses selection of suitable coformers, mechanistic aspects of solubility enhancement, characterization techniques, regulatory considerations, and reported literature on zolmitriptan solid-state modification.[8–11] Current challenges, future perspectives, and research gaps related to zolmitriptan cocrystals are also highlighted. The review aims to provide a comprehensive scientific foundation for researchers exploring cocrystallization as a novel and effective strategy for improving the biopharmaceutical performance of zolmitriptan.

KEYWORDS: Zolmitriptan; pharmaceutical cocrystals; solubility enhancement; dissolution rate; crystal engineering; migraine therapy.

1. INTRODUCTION

Oral drug delivery remains the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness.[12] However, the successful development of oral dosage forms is often limited by the poor aqueous solubility of many drug candidates. It has been reported that nearly 40–60% of newly discovered chemical entities suffer from low solubility, leading to inadequate dissolution in gastrointestinal fluids and poor oral bioavailability.[13,14]

Zolmitriptan is a second-generation triptan indicated for the acute treatment of migraine attacks. Despite its potent pharmacological activity and favorable permeability, its limited aqueous solubility poses formulation challenges, particularly when rapid onset of action is desired.[3,15] Conventional approaches such as salt formation, particle size reduction, solid dispersions, and use of surfactants have been explored to overcome solubility issues; however, each method has inherent limitations related to stability, manufacturability, or regulatory acceptability.[16–18]

In recent years, pharmaceutical cocrystals have gained considerable attention as a versatile and robust solid-state modification strategy. By forming a crystalline complex of the API with a suitable coformer through non-covalent interactions, cocrystals can significantly alter solubility, dissolution rate, mechanical properties, and stability of drugs.[5,6,19] This review focuses on the role of cocrystallization as a novel approach for enhancing the solubility and dissolution rate of zolmitriptan.

2. Zolmitriptan: Drug Profile

2.1 Chemical Structure and Physicochemical Properties

Zolmitriptan is chemically designated as (S)-4-{[(3-(2-dimethylaminoethyl)-1H-indol-5-yl)methyl]-1,3-oxazolidin-2-one}.[20] It is a weakly basic compound containing indole and tertiary amine functionalities, which play a crucial role in its intermolecular interactions and solid-state behavior.[21]

Key physicochemical properties of zolmitriptan include moderate lipophilicity, low aqueous solubility, and good membrane permeability. These properties categorize zolmitriptan under BCS class II, where dissolution is the rate-limiting step for absorption.[22,23]

2.2 Pharmacology and Therapeutic Use

Zolmitriptan exerts its antimigraine effect by selective agonism at serotonin 5-HT1B and 5-HT1D receptors, leading to cranial vasoconstriction and inhibition of neuropeptide release.[24] Rapid dissolution and absorption are essential for prompt relief from migraine symptoms, making solubility enhancement a critical formulation objective.[25]

2.3 Limitations Related to Solubility

The low intrinsic solubility of zolmitriptan can result in delayed onset of action and inter-individual variability in therapeutic response.[26] Therefore, novel formulation strategies are required to improve its dissolution characteristics without compromising chemical stability or safety.

3. Pharmaceutical Cocrystals: An Overview

3.1 Definition and Concept

Pharmaceutical cocrystals are crystalline materials composed of an API and one or more neutral coformers in a definite stoichiometric ratio, bonded through non-covalent interactions such as hydrogen bonding, π–π stacking, or van der

Waals forces.[5,7] Unlike salts, cocrystals do not involve proton transfer, making them suitable for APIs with limited ionizable groups.[27]

3.2 Historical Development of Cocrystals

The concept of cocrystals originated in the field of supramolecular chemistry and crystal engineering. Over the last two decades, their application in pharmaceutical sciences has expanded significantly due to their ability to tailor drug properties at the molecular level.[28,29]

3.3 Classification of Cocrystals

Cocrystals can be classified based on the nature of the coformer, stoichiometric ratio, and type of intermolecular interactions. Common categories include API–API cocrystals, API–coformer cocrystals, and multicomponent cocrystals.[30]

4. Rationale for Cocrystallization of Zolmitriptan

Zolmitriptan possesses functional groups capable of forming strong hydrogen bonds, making it a suitable candidate for cocrystal formation.[21,31] Cocrystallization can modify its crystal lattice energy, improve wettability, and enhance interaction with dissolution media, ultimately leading to increased solubility and dissolution rate.[6,32]

5. Selection of Coformers for Zolmitriptan Cocrystals

5.1 Criteria for Coformer Selection

The selection of an appropriate coformer is a critical step in cocrystal design. Coformers should be pharmaceutically acceptable, non-toxic, and capable of forming predictable intermolecular interactions with zolmitriptan.[33] Generally Recognized as Safe (GRAS) compounds such as organic acids, amides, and polyphenols are commonly employed.[34]

5.2 Supramolecular Synthon Approach

The supramolecular synthon concept aids in rational cocrystal design by identifying complementary functional groups between the API and coformer.[35] Zolmitriptan can form robust heterosynthons through hydrogen bonding between its amine or carbonyl groups and coformer functionalities.[36]

6. Methods of Preparation of Zolmitriptan Cocrystals

Cocrystals of zolmitriptan can be prepared using various techniques such as solvent evaporation, neat grinding, liquid-assisted grinding, slurry conversion, spray drying, and hot melt extrusion.[37–40] Each method offers distinct advantages and limitations in terms of scalability, crystal habit control, and reproducibility.

7. Characterization of Zolmitriptan Cocrystals

Comprehensive solid-state characterization is essential to confirm cocrystal formation and evaluate physicochemical properties. Commonly employed techniques include powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FTIR), solid-state nuclear magnetic resonance (SSNMR), and scanning electron microscopy (SEM).[41–45]

8. Mechanisms of Solubility and Dissolution Enhancement

Cocrystals enhance solubility through lattice energy reduction, improved wettability, and favorable intermolecular interactions with solvent molecules.[6,32] The presence of hydrophilic coformers plays a significant role in accelerating dissolution and maintaining supersaturation.[46]

9. Review of Literature on Zolmitriptan Solid-State Modifications

Several studies have reported solid-state modifications of zolmitriptan, including salts and polymorphs, to improve its solubility and dissolution behavior.[47–49] Although limited reports are available on zolmitriptan cocrystals, analogous studies on indole-based and triptan-class drugs demonstrate the strong potential of cocrystallization for this molecule.[50–52]

10. Regulatory and Intellectual Property Aspects

Regulatory agencies such as the US FDA and EMA recognize pharmaceutical cocrystals as distinct solid forms of APIs.[53] From an intellectual property perspective, cocrystals provide opportunities for patent protection and lifecycle management of existing drugs.[54,55]

11. Challenges in Development of Zolmitriptan Cocrystals

Despite their advantages, challenges associated with zolmitriptan cocrystals include coformer selection, scale-up feasibility, physical and chemical stability, and establishment of in vitro–in vivo correlation.[56,57]

12. Future Perspectives

Advanced computational modeling, crystal structure prediction, and high-throughput screening techniques are expected to accelerate the development of zolmitriptan cocrystals.[58] Integration of cocrystal technology with novel drug delivery systems may further enhance therapeutic outcomes.[59]

13. CONCLUSION

Pharmaceutical cocrystallization represents a promising and scientifically sound approach to overcome the solubility limitations of zolmitriptan. Rational selection of coformers and appropriate preparation methods can significantly enhance dissolution rate and potentially improve oral bioavailability and therapeutic efficacy.[6,32,60]

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