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Optimizing the Therapeutic Potential of Sacubitril/Valsartan: The Promise of Co-Crystal Engineering

Sharma R*

Director and Lead Consultant, Department of Cardiology, Heart Rhythm Services & Cardiac pacing Division, Fortis Hospital Mohali, Punjab, India

***Corresponding author:** Rajat Sharma, Director and Lead Consultant, Department of Cardiology, Heart Rhythm Services & Cardiac pacing Division, Fortis Hospital Mohali, Punjab, India, Tel: 8283812952; Email: rajat.dr@gmail.com

Short communication

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Abstract

Heart failure (HF) is a complex clinical syndrome with high morbidity and mortality, posing a significant global healthcare burden. Guideline-directed medical therapy remains the standard for managing HF with reduced ejection fraction (HFrEF), incorporating four key drug classes, including angiotensin receptor–neprilysin inhibitors (ARNIs). Sacubitril/valsartan (Entresto, development code LCZ696) was approved as the first successful angiotensin receptor neprilysin inhibitor (ARNI) in the market in 2015 and has demonstrated efficacy in treating HF. The sacubitril/valsartan combination was developed by Novartis and marketed by JB Chemicals as Azmarda (Innovator Sacubitril/Valsartan) in India. The co-crystal technology utilized in the innovator's Sacubitril/Valsartan formulation, enhances its solubility, stability, and bioavailability, thereby optimizing therapeutic effectiveness. Co-crystal technology offers advantages over generic formulations by improving drug dissolution, permeability, and pharmacokinetics. A recent study comparing different sacubitril/valsartan brands highlights the superior dissolution characteristics and stability of co-crystal formulations, such as Azmarda, which utilize a patented polymorphic technology. As HF treatment continues to evolve, integration of innovative co-crystal technology in drug formulations represents a promising approach to enhancing drug performance and improving patient outcomes.

Keywords: Heart Failure; Co-Crystal Technology; Sacubitril/Valsartan; Bioavailability; Angiotensin Receptor-Neprilysin Inhibitors

Abbreviations

HF: Heart failure; HFrEF: Heart Failure with Reduced Ejection Fraction; ARNI: Angiotensin Receptor Neprilysin Inhibitor; BCS: Biopharmaceutical Classification System; FDA: Food and Drug Administration; ARNIs: Angiotensin receptor–neprilysin inhibitors.

Introduction

Heart failure (HF) is a complex clinical syndrome that eventually affects multiple organs and systems in the body, leading to increased morbidity and mortality. It is a major global public health concern due to its high prevalence, significant mortality rates, and substantial healthcare

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costs [1]. Guideline-directed medical therapy serves as the standard pharmacological approach for managing HF with reduced ejection fraction (HFrEF) and comprises four key drug classes, including Angiotensin receptor–neprilysin inhibitors (ARNIs), β-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter 2 inhibitors [2].

Angiotensin receptor–neprilysin inhibitor is a novel class of medications used in the management of HF. Sacubitril/valsartan, a leading ARNI, combines a neprilysin inhibitor with an angiotensin receptor blocker (ARB) [3] and is specifically recommended for the treatment of patients with symptomatic HF [4]. In 2015, the U.S. Food and Drug Administration (FDA) and the European Medicines Agency approved sacubitril/valsartan as the first commercially available ARNI [5]. Novartis developed the sacubitril/valsartan combination, which is marketed in India by JB Chemicals under the brand name Azmarda (Innovator Sacubitril/Valsartan). The polymorphic technology used in Azmarda, manufactured by innovator company, has been patented and recognized.

Sacubitril/valsartan marketed as Azmarda (manufactured by the innovator company) is a cocrystal consisting of six sacubitril and six valsartan moieties in their anionic forms, 18 penta- and hexa- coordinated sodium cations, and 15 water molecules. This cocrystal formulation is the one that has been tried and proven effective in RCTs. After the expiry of patent several pharmaceutical companies have implemented alternative strategies to incorporate sacubitril/valsartan into their products using varied manufacturing processes. One such approach includes the use of a fixed-dose combination of sacubitril/valsartan [6].

Valsartan, a Biopharmaceutical Classification System (BCS) Class II drug, is characterized by low solubility and high permeability [7]. This classification indicates that the bioavailability of oral dosage forms is constrained by dissolution rate. Sacubitril/valsartan are highly hygroscopic and challenging to handle in their amorphous (non-crystalline) form, which can negatively impact their in vitro and in vivo performance, as well as raise storage concerns. The effectiveness of drug is influenced by several factors, such as its solubility, stability, dissolution rate, and hygroscopicity. Current research focuses on improving oral absorption of drugs with poor water solubility and/or limited permeability, with pharmaceutical cocrystals emerging as a promising approach to enhance bioavailability [6]. In recent years, pharmaceutical co-crystals have gained significant attention as a promising green and sustainable approach to enhancing the solubility, stability, and bioavailability of poorly soluble drugs [8].

Co-crystal formation is a modern strategy to enhance key properties of a drug, including solubility, stability, melting point, pharmacokinetics, pharmacodynamics, and bioavailability. Co-crystals are single-phase crystalline structures composed of two or more distinct molecular components in a fixed stoichiometric ratio, helping to optimize drug performance [9]. Unlike covalent modifications, co-crystals enable the alteration of physicochemical properties without changing the drug's molecular structure. Recognizing their potential, the FDA now considers drug products containing novel co-crystals analogous to new polymorphic forms of an active pharmaceutical ingredient. This regulatory shift, along with the successful commercialization of sacubitril/valsartan co-crystal, has brought significant attention to co-crystals in both industry and academia [10].

Over the past few years, there has been a significant increase in focus on pharmaceutical co-crystals, highlighting their potential in drug formulation and development [11]. However, the absence of crystal lattice structures among generic products may affect their bioavailability and pharmacokinetics, underscoring the need for careful selection of crystal forms in drug development to ensure therapeutic effectiveness [6]. Enhancing solubility can lead to improved bioavailability, minimize variability in therapeutic effects, and ultimately enhance patient safety and treatment effectiveness [12]. Therefore, developing formulations that improve bioavailability is not just a technical challenge but a crucial aspect of effective drug design.

A focused review discussed the challenges and opportunities of pharmaceutical co-crystals, highlighting their potential to enhance mechanical properties, hydration stability, solubility, bioavailability, and permeability of drugs. The sacubitril/valsartan developed by the innovator has been cited as a successful example of co-crystal technology in cardiovascular therapy [13]. In line with this, a study analyzed 16 different brands of sacubitril/valsartan tablets, including the reference product Azmarda, manufactured by innovator company, using methods such as differential scanning calorimetry, powder X-ray diffraction, sodium content analysis, and dissolution testing. The findings indicated that Azmarda, formulated using co-crystal technology, exhibited superior dissolution characteristics, distinctive crystal lattice structures, unique melting pattern and optimized sodium content. These results highlight the potential advantages of this innovative formulation compared to other marketed products. This study was focused on a specific number of brands, and the generalizability of the findings to all sacubitril/valsartan formulations may be limited. [6].

Heart failure management continues to evolve, with sacubitril/valsartan representing a major breakthrough in treatment. However, optimizing its formulation through innovative technologies like co-crystal technology can

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further enhance its therapeutic potential. By improving solubility, stability, and bioavailability, co-crystal formulations offer a promising approach to more effective and patient-friendly treatment options. A study analyzing various sacubitril/valsartan formulations demonstrated that the innovative cocrystal technology used in Azmarda tablets provides superior dissolution properties, optimized sodium content, thermal stability, and unique crystal lattice structures compared to various marketed products. As research progresses, integrating co-crystal technology into pharmaceutical formulations may redefine cardiovascular drug therapy, offering new hope for HF patients worldwide.

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Declaration

Conflict of Interest: No conflict of interest to declare.

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