MedCrave
Step into the World of Research

Pharmacy & Pharmacology International Journal

Short Communication

Open Access

CrossMark

Unlocking the polymorphic odyssey of Rivaroxaban: a journey of pharmaceutical innovation

Abstract

The field of pharmaceutical science is a dynamic landscape driven by the pursuit of enhanced drug formulations and improved therapeutic outcomes. One remarkable journey within this domain is the polymorphism odyssey of rivaroxaban, a distinguished anticoagulant inhibitor targeting blood coagulation factor Xa. Rivaroxaban plays a key role in the prevention and treatment of thromboembolic disorders, including myocardial infarction, stroke, and deep venous thromboses. Its intricate crystal structures and diverse solid-state forms, each imparting unique properties affecting solubility, bioavailability, and stability, illuminate the challenges, breakthroughs, and relentless pursuit of superior drug performance in the pharmaceutical development of rivaroxaban. This work not only reflects the scientific commitment to enhancing therapeutic efficacy but also underscores the dynamic interplay between chemical innovation and clinical application in drug development.

Keywords: rivaroxaban, crystal structures, patent innovation, commercial viability, synthesis, pharmaceutical science

Volume 12 Issue 2 - 2024

Renan Marcel Bonilha Dezena,[1] Paulo César Pires Rosa[2]

[1]Preformulation Specialist Consultant, Pharmaceutical Industry, Brazil, Faculty of Pharmaceutical Sciences (Special Graduate Student), University of Campinas (UNICAMP), Brazil

[2]Faculty of Pharmaceutical Sciences, University of Campinas (UNICAMP), Brazil

Correspondence: Renan Marcel Bonilha Dezena, Preformulation Specialist Consultant, Pharmaceutical Industry, Brazil, Faculty of Pharmaceutical Sciences (Special Graduate Student), University of Campinas (UNICAMP), Brazil, Email renan_marcel@hotmail.com

Received: March 25, 2024 | **Published:** April 22, 2024

Background

The field of pharmaceutical science is in a constant state of evolution, driven by the quest for improved drug formulations and therapeutic outcomes. One remarkable chapter in this saga is the polymorphism odyssey of rivaroxaban, a notable anticoagulant inhibitor of blood coagulation factor Xa with enhanced selectivity developed to the prophylaxis and treatment of various thromboembolic disorders, including myocardial infarction, stroke, and deep venous thromboses.[1,2]

With its complex crystal structures and distinct solid-state forms (each possessing distinct properties that influence solubility, bioavailability, and stability), rivaroxaban's journey through the realm of pharmaceutical development unveils challenges, breakthroughs, and the pursuit of enhanced drug performance.[3]

This work not only reflects the scientific commitment to enhancing therapeutic efficacy but also underscores the dynamic interplay between chemical innovation and clinical application in drug development.

Expanding horizons through patent innovations

The scientific realm is never linear, and rivaroxaban's path unfolds against the backdrop of the US Patent number 7.585.860.[4] This patent uncovers substituted oxazolidinone derivatives and their salts, expanding the horizons of anticoagulant research.[4] The most successful approach in the realm of anticoagulant drug discovery, particularly focusing on a 1,3-substituted heterocycle core, culminated in the discovery of the oxazolidinone class and to enhance its properties, researchers introduced an isoindoline core and replaced the highly basic amidinomethoxy moiety with a 4-pyridylaminomethyl group.[5] While this alteration significantly improved FXa affinity, challenges related to oral bioavailability prompted further refinements.[5] In a bid to optimize the compound, researchers strategically incorporated the chlorothiophene P1 moiety into another oxazolidinone-containing hit.[5] The iterative process of refinement continued with the replacement of the P4 thiomorpholine moiety with a morpholine group.[5] The exploration of various heterocyclic P4 modalities expanded the possibilities, ultimately resulting in the discovery of the lactam analogue with a remarkable FXa IC50.[5] However, a turning point in the development process occurred with the introduction of a carbonyl moiety into the morpholine P4 group, giving rise to compound, widely known as rivaroxaban.[5]

Rivaroxaban emerges as an Xa inhibitor with heightened selectivity, transforming the landscape of thromboembolic disorder treatments.[6]

Real-world applications and synthesis

The pharmacological stage is often set by patents, but the true performance of a drug is unveiled in its real-world applications. Rivaroxaban, marketed as Xarelto®, arrives as a tablet containing 10 mg of the precious compound.[7] The intricate processes for rivaroxaban's preparation and its intermediates are detailed in US Patent numbers 7.585.860, 7.351.823, and 7.816.355, along with a multitude of patent cooperation treaty (PCT) publications and academic literature.

Each step in the synthesis contributes to the final masterpiece – a therapeutic agent offering hope to those afflicted by thromboembolic disorders.[7–9]

Polymorphism

Polymorphism emerges, introducing variability in rivaroxaban's crystal structures. This anticoagulant, renowned for its therapeutic potential, initially presented three polymorphic forms: modification I, modification II, and modification III, as intricately elucidated within the annals of the distinguished WO 2007/039132 patent (Table 1). These forms have beckoned researchers to unlock their structural secrets and transform the landscape of drug development.[10]

Beyond these forms, a captivating ensemble of variations steps into the spotlight, including a hydrate variant, an NMP solvate, a THF-clathrate, and the elusive amorphous incarnation of rivaroxaban (Table 1).

Table 1 Compiled of endothermic, exothermic, glass transition and mass loss events of polymorphs described in the literature.[10,11]

Polymorphs	DSC (Endothermic)	DSC (Exothermic)	DSC (Glass Transition)	TGA (Mass Loss)
Modification I	232.9°C	-	-	0.10%
Modification II	235.0°C	205.8°C	-	0.10%
Modification III	235.0°C	151.7°C	-	< 0.5 %
Hydrate	234.8°C	153.8°C	-	4%
Dihydrate	84.3°C	149.0°C		7.70%
	232.5°C			
NMP solvate	115.5°C	121.7°C	-	18.50%
	175.4°C			
	235.0°C			
THF-clathrate	59.4°C	-	-	5 - 7%
	179.2°C			
	232.8°C			
Amorphous	-	-	83°C	-

*The values obtained from the images of the DSC curves of the WO 2007/039132 patent using WebPlotDigitalizer tool.[12]

Here, the focus is on the distinct solubility advantages of modification II and the amorphous form, positioning them as the forefront of future drug formulations.[10,13] Their inherent solubility properties promise rapid drug absorption and consistent therapeutic outcomes. Notably, modification II emerges as a strategic choice with a solubility quotient four times greater than its predecessor, modification I, igniting possibilities for unprecedented pharmaceutical formulations.[10,14]

Curiously, despite its superior solubility, the preferred modification II has yet to find its place in the realm of currently marketed oral dosage forms of rivaroxaban. This stands in stark contrast to the less soluble modification I. The complexity of producing modification II at a commercial scale could be one possible explanation. The procedures delineated in W02007/039132 patent involve the evaporation of a rivaroxaban solution in 1,4-Dioxan or shock-cooling-processes that pose challenges in large-scale implementation.[10]

As the quest for enhanced solubility persists, the demand for a novel polymorphic form of rivaroxaban takes center stage. This form not only surmounts the solubility limitations of modification I, but also presents a promise of feasibility in large-scale production. Bridging this gap requires an innovative approach that marries enhanced solubility with practicality.[10]

These diverse forms become a focal point, as their characteristics influence drug performance. While modification II's enhanced solubility shines bright, modification I take center stage in marketed oral dosage forms due to its favorable bioavailability. The quest for the perfect polymorphic form adds layers to rivaroxaban's saga.[10]

Crystal forms and enhanced selectivity

In the annals of pharmaceutical innovation, the patent number WO2015111076A2 ushers in improved processes for crafting the pure crystal modification I of rivaroxaban – a form that stands free from unwanted polymorphs and solvated derivatives (Figure 1). Rivaroxaban's potential as a clotting factor Xa inhibitor for conditions like myocardial infarction, stroke, and more, has been the driving force behind these advancements. The patent, while heralding the commercial viability and industrial advantages of this crystalline form, points towards an ongoing scientific journey.[15]

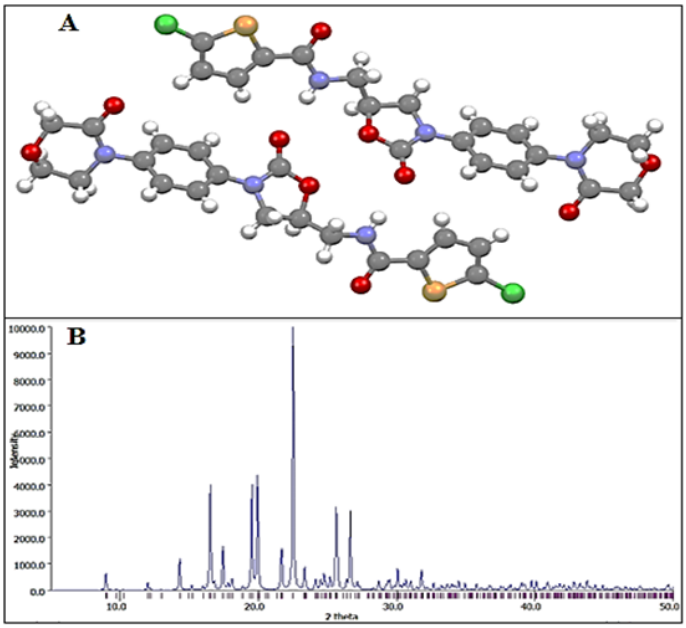

Figure 1 A Asymmetrical unit containing two distinct rivaroxaban molecules, each adopting a different conformation (cambridge crystallographic data center deposition number 1810879 using Mercury software, version 3.7).[15,16]

B - X-ray diffraction profile of rivaroxaban (cambridge crystallographic data center deposition number 1810879 using Mercury software, version 3.7) similar to form I available in patent number WO2015/111076A2.[15,16]

Novel crystalline dihydrate

Rivaroxaban was initially dissolved in formic acid, resulting in the formation of a crystalline formic acid solvate. This intermediate compound was further transformed into the dihydrate by suspending it in water at ambient temperature. Stirring the suspension allowed the conversion to occur, with the pH optionally adjusted using a suitable base. The dihydrate was subsequently isolated through filtration or centrifugation.[17]

One of the most significant findings regarding the crystalline dihydrate of rivaroxaban is its substantially improved solubility

Citation: Dezena RMB, Rosa PCP. Unlocking the polymorphic odyssey of Rivaroxaban: a journey of pharmaceutical innovation. *Pharm Pharmacol Int J.* 2024;12(2):65–67. DOI: 10.15406/ppij.2024.12.00434

compared to other forms, particularly the widely used form I of rivaroxaban. This enhancement in solubility, which translates to improved bioavailability, is crucial for ensuring the drug's efficacy in anticoagulation therapy.[17]

The discovery of the crystalline dihydrate of rivaroxaban opens the door to the development of new pharmaceutical formulations with improved bioavailability. These formulations may include tablets, capsules, sachets, or suspensions designed for various routes of administration, such as oral, parenteral, or transdermal. The potential to control drug release rates further enhances the versatility of this novel compound.[17]

The crystalline dihydrate of rivaroxaban exhibits polymorphic stability when stored under appropriate conditions, remaining unchanged even after extended periods. It is vital for pharmaceutical compositions to maintain their stability during storage to ensure consistent drug efficacy. Special precautions are necessary to avoid the transformation of the dihydrate into other polymorphic forms, particularly in low-humidity environments.[17]

Unlocking amorphous potential

Amidst the challenges of obtaining high purity and stability, researchers embark on a new phase. The pursuit of amorphous coprecipitates of rivaroxaban with specific excipients comes to the fore. The goal is to harness the potential of amorphous forms, known for their improved dissolution rates and bioavailability. These coprecipitates are remarkably stable and do not tend to convert into crystalline forms over time, ensuring consistent drug performance throughout its shelf life and the coprecipitates are highly pure, with minimal impurities or crystalline forms.[11]

The preparation process for these coprecipitates is consistently reproducible, providing pharmaceutical manufacturers with a dependable method for producing high-quality formulations.[11]

Through meticulous experimentation, the link between hypromellose phthalate and rivaroxaban's amorphous coprecipitates emerges, presenting itself as a potential alternative in formulation design.[11]

Summary

Rivaroxaban's polymorphism odyssey highlights the importance of pharmaceutical innovation. From crystal structures to dissolution rates, each facet contributes to the growth of knowledge. As researchers continue to unravel the mysteries of polymorphism and solid-state forms, the journey towards safer, more effective drug formulations remains ongoing.

The convergence of scientific breakthroughs with practical feasibility charts a course toward the future of pharmaceuticals. This odyssey is more than the discovery of novel forms; it signifies the potential to reshape the development of new formulations.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Alam P, Ezzeldin E, Iqbal M, et al. Ecofriendly densitometric RP-HPTLC method for determination of rivaroxaban in nanoparticle formulations using green solvents. *RSC Adv*. 2020;10(4):2133–2140.
2. Süslü İ, Çelebier M, Altınöz S. Electrochemical behaviour investigation and square-wave voltammetric determination of rivaroxaban in pharmaceutical dosage forms. *Anal Methods*. 2014;6(23):9397–9403.
3. Themed issue: Polymorphism and crystal forms. *New J Chem*. 2008;32(10):1657.
4. Straub A, Lampe T, Pohlmann J, et al. *Substituted oxazolidinones and their use in the field of blood coagulation*. US Patent. 7585860, 2009.
5. Pinto DJP, Smallheer JM, Cheney DL, et al. Factor Xa inhibitors: next-generation antithrombotic agents. *J Med Chem*. 2010;53(17):6243–6274.
6. Zhou Q, Bea F, Preusch M, et al. Evaluation of plaque stability of advanced atherosclerotic lesions in APO E-deficient mice after treatment with the oral factor xa inhibitor rivaroxaban. *Mediators Inflamm*. 2011;2011:432080.
7. Mladentsev DY, Kuznetsova EN, Skvortsova MN, et al. Review on synthetic approaches toward rivaroxaban (xarelto), an anticoagulant drug. *Org Process Res Dev*. 2022;26(8):2311–2329.
8. Berwe M, Thomas C, Rehse J, et al. *Preparation process*. US Patent. 7351823, 2008.
9. Bodhuri P, Weeratunga G. *Processes for the preparation of rivaroxaban and intermediates thereof*. US Patent. 7816355, 2010.
10. Grunenberg A, Lenz J, Braun GA, et al. *Novel polymorphous form and the amorphous form of 5-chloro-n-({ (5s)-2-oxo-3-[4-(3-oxo-4-morpholinyl)-phenyl]-1,3-oxazolidine-5-yl}-methyl)-2-thiophene carboxamide*. World Patent. 2007039132:A1, 2007.
11. Rao DM, Reddy BV. *Amorphous coprecipitates of rivaroxaban*. World Patent. 2014016842:A1, 2014.
12. Rohatgi A. WebPlotDigitizer: Web Based Tool to Extract Data from Plot, Images, and Maps. Version 4.6. 2022.
13. Choi M-J, Woo MR, Choi H-G, et al. Effects of polymers on the drug solubility and dissolution enhancement of poorly water-soluble rivaroxaban. *Int J Mol Sci*. 2022;23(16):9491.
14. Zhai J, Chen Z, Liu X, et al. Solubility measurement, model evaluation and thermodynamic analysis of rivaroxaban polymorphs in organic solvents. *J Chem Thermodyn*. 2017;104:218–229.
15. Rao DM, Venugopal B. *Improved processes for the preparation of highly pure rivaroxaban crystal modification i*. World Patent. 2015111076:A2, 2015.
16. Shen J, Tang G-P, Hu X-R. Crystal structure of (S)-5-chloro-N-(2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-5-ylmethyl)thiophene-2-carboxamide. *Acta Crystallogr E Crystallogr Commun*. 2018;74(1):51–54.
17. Ludescher J. *Crystalline form of rivaroxaban dihydrate*. World Patent. 2012004245:A1, 2012.

Citation: Dezena RMB, Rosa PCP. Unlocking the polymorphic odyssey of Rivaroxaban: a journey of pharmaceutical innovation. *Pharm Pharmacol Int J*. 2024;12(2):65–67. DOI: 10.15406/ppij.2024.12.00434