https://doi.org/10.31925/farmacia.2025.1.1 **REVIEW**

AN OVERVIEW OF THE PHARMACEUTICAL PROFILE OF RIVAROXABAN

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Abstract

The first approved orally active direct inhibitor of factor Xa is rivaroxaban (RIV). The main topics of this review include the pharmacological profile, physicochemical properties, methods to improve water solubility and pharmaceutical dosage forms developed in various recent studies. New approaches have been designed to increase the low solubility of rivaroxaban. These technologies, which range from conventional dosage forms to drug delivery systems with nanoparticles, can potentially enhance bioavailability and thus therapeutic efficacy. The literature search revealed that several methodologies were applied depending on the aim of the study, since the physicochemical properties of RIV allow its incorporation into different pharmaceutical systems.

Rezumat

Primul inhibitor direct al factorului Xa, activ oral, aprobat, este rivaroxabanul (RIV). Principalele subiecte ale prezentului studiu includ profilul farmacologic, proprietățile fizico-chimice, metodele de îmbunătățire a solubilității în apă și formele farmaceutice de dozare dezvoltate în diferite studii recente. Au fost concepute noi abordări pentru a crește solubilitatea scăzută a rivaroxabanului. Aceste tehnologii, care variază de la forme de dozare convenționale la sisteme de administrare a medicamentelor cu nanoparticule, pot îmbunătăți biodisponibilitatea și, prin urmare, eficacitatea terapeutică. Cercetările literaturii de specialitate au relevat că au fost aplicate mai multe metodologii în funcție de scopul studiului, întrucât proprietățile fizico-chimice ale RIV permit încorporarea acestuia în diferite sisteme farmaceutice.

Keywords: rivaroxaban, oral anticoagulants, pharmacological profile, low solubility

Introduction

Venous thromboembolism (VTE) is a serious condition that poses a significant public health problem due to the considerable morbidity and mortality associated with it [21]. Blood clots in the veins are referred to as VTE. Every year, almost 10 million people worldwide suffer from venous thromboembolism, a chronic disease that includes both pulmonary embolism (PE) and deep vein thrombosis (DVT). Venous stasis or reduced blood flow in the vessels causes VTE, which in turn causes fibrin and platelet aggregation and thrombosis [22, 69]. Once DVT occurs, it is likely to cause PE and be fatal [75]. Venous and arterial thromboembolic diseases are prevented and treated with anticoagulants. The basic treatment is known to consist initially of parenteral administration of anticoagulants, followed by long-term oral administration of vitamin K antagonists [4, 29]. At the beginning of the 20th century, unfractionated heparin and warfarin - the first anticoagulant drugs for the prevention of VTE - were discovered by chance [48, 72]. These drugs were improved in the following years to prevent or cure VTE even more effectively. Coagulation factor IIa (thrombin) and coagulation factor Xa (FXa), two enzymes essential for blood clotting, are the targets of a new class of anticoagulant drugs that have recently been developed [28, 31].

For nearly all patients with VTE, direct oral anticoagulants (DOACs) constitute the first line of treatment, but low molecular weight heparins are still commonly used [77]. For individuals with VTE caused by a significant transient risk factor, anti-coagulation may be discontinued after the first three to six months of treatment. Indefinite anticoagulant medication is recommended for patients in whom the long-term risk of recurrent venous thromboembolism is higher than the long-term risk of significant bleeding, such as those with spontaneous venous thromboembolism or with active malignant disease. For patients having major orthopaedic or cancer surgery, pharmacological prevention of VTE is usually required [39].

In the last 20 years, the activated serine protease factor Xa has become the focus of research into new

anticoagulant medications and has garnered a lot of attention.

Nevertheless, several studies with novel oral anticoagulants have shown that factor Xa inhibitors are effective in VTE by reducing thrombin production, which in turn reduces thrombin-mediated platelet activation and coagulation without affecting the activity of pre-existing thrombin. [34, 58].

Rivaroxaban (RIV) is the first direct, non-cofactor-dependent inhibitor of specific factor Xa to be approved as a drug for humans [37].

Rivaroxaban was patented by Bayer HealthCare in 2007 and is the first synthetic oral anticoagulant that selectively binds to the active site of factor Xa and reversibly inhibits it [54]. It was approved in 2008 by the European Commission and Health Canada, under its original name Xarelto®, for clinical use in the prevention of VTE, DVT and PE following elective hip or knee replacement. It was first approved by the FDA in 2011, so it was not available as a generic until 2024 [65]. Due to its effectiveness and popularity, it is included in the World Health Organization's list of essential medicines [73].

Subsequently, more oral direct factor Xa inhibitors were synthetized and are now used as human medicines. The direct factor Xa inhibitors (xabans) currently approved by European Medicines Agency (EMA) and U.S. Food and Drug Administration (FDA) are listed in Table I.

Table I

Direct factor Xa inhibitors (xabans) with marketing authorization [32, 33]

Active	***Original product/ manufacturer***	***Pharmaceutical form***	***Dosages***	***Approved by - year of approval***
Rivaroxaban	Xarelto®/Bayer HealthCare, Germany	Film-coated tablets	2,5 mg 10 mg 15 mg 20 mg	EMA - 2008 FDA - 2011
		Granules for oral suspension	1mg/ml when reconstituted	
Apixaban	Eliquis®/Bristol-Myers Squibb, USA	Film-coated tablets	2.5 mg 5 mg	EMA - 2011 FDA - 2012
		Granules in capsule for opening	0.15 mg	
		Coated granules	0.5 mg 1.5 mg 2 mg	
Edoxaban	Lixiana®/Daiichi Sankyo Company, Limited, Japan	Film-coated tablets	15 mg 30 mg 60 mg	EMA - 2015
	Roteas®/Daiichi Sankyo Europe GmbH, Germany			EMA - 2017
	SAVAYSA®/Daiichi Sankyo Europe GmbH, Germany			FDA - 2015
Betrixaban	Bevyxxa®/Portola Pharmaceuticals, USA	Capsules	40 mg 80 mg	FDA - 2017
	Dexxience®/Portola Pharmaceuticals, USA			EMA - refusal of marketing authorization 2018

Over time, other xabans were developed but did not reach the market, such as darexaban from Astellas Pharma Inc., Japan [25], otamixaban from Sanofi S.A., France [6], letaxaban from Takeda Pharmaceutical Company Limited, Japan [12] and eribaxaban from Pfizer Inc., the USA [15]. In 2021, the EMA approved the first generic for rivaroxaban.

Studies have shown that all factor Xa inhibitors have similar rates of stroke or systemic embolism, but rivaroxaban has a higher risk of major bleeding than the others [34].

Pharmacological profile of rivaroxaban

Factor Xa is a key enzyme in the blood clotting process and plays a central role in both the intrinsic and extrinsic pathways that lead to the formation of blood clots. This factor helps in the conversion of prothrombin to thrombin, a critical step that enables the formation of fibrin so that blood clots are stabilized. Rivaroxaban is an oral direct anticoagulant (DOACs) [55]. In addition, rivaroxaban is an oral, direct, reversible, competitive, rapid and dose-dependent inhibitor of FXa [27]. Given its mechanism of action, rivaroxaban therefore causes inhibition of thrombin generation and prolongation of prothrombin time [30]. Due to its predictable pharmacokinetics and pharmaco-dynamics, the pharmacological effect of rivaroxaban is closely related to plasma concentrations in healthy volunteers [59], whereby rivaroxaban is an effective, well-tolerated [41], safe and specific inhibitor of factor Xa. Table II lists the diseases or conditions for which rivaroxaban is indicated.

Table II

Indications of rivaroxaban

Labeled indications	**Prevention of VTE [71]**
	Treatment of DVT and PE [26, 66]
	Non-valvular atrial fibrillation (NVAF) [57]
	Acute Coronary Syndrome (ACS) [49]
Off-label indications	Management of left ventricular thrombi [10]
	Prevention of thrombosis in cancer patients [38]
	Atrial fibrillation and stroke prevention [60]
	Extended anticoagulation post-surgery [35]

Rivaroxaban has predictable pharmacokinetics that follow a one-compartment oral model [53]. Factors such as age, renal function, body weight and gender influence its pharmacokinetics, resulting in moderate variability. This suggests that a fixed dosing regimen may be appropriate for many patients.

Rivaroxaban is rapidly absorbed and reaches its maximum plasma concentration approximately 2 - 4 hours after administration [26]. When taken orally, bioavailability is around 80 % [44], but can be influenced by food. It is therefore important that the drug dose is administered consistently and evenly under the same conditions in order to achieve an optimal effect and avoid fluctuations that could impair the effectiveness of the treatment.

Oxidative degradation *via* CYP450 and CYP-independent hydrolysis of amide bonds are the two main pathways for the metabolism of rivaroxaban. In addition, rivaroxaban is mainly excreted renally (66%), whereby the proportion of faecal/biliary excretion is significantly lower [8].

When administered concomitantly with medicinal products that inhibit or induce the CYP3A4 isoform or with P-gp inhibitors [45], the active substance levels of rivaroxaban may be altered, which affects its efficacy and safety.

Due to the decrease of renal function of elderly patients, age affects the pharmacokinetics of rivaroxaban, resulting in higher plasma concentrations and increased drug exposure. Furthermore, gender has only a minimal effect on the PK of rivaroxaban [42].

As rivaroxaban is excreted via the kidneys, chronic renal failure may lead to problems that require dose adjustment [13] depending on creatinine clearance.

Bleeding complications are the most important and most frequently reported adverse effects [74]. Rivaroxaban is associated with an increased risk of bleeding, which is particularly high in certain population groups such as the elderly, patients with kidney disease, severely overweight or underweight patients or patients with chronic liver disease [7]. The contraindications for rivaroxaban [65] are summarized in Table III.

Table III

Contraindications for rivaroxaban

Significant	allergy to rivaroxaban
	active an uncontrolled bleeding
Others	antiphospholipid syndrome
	chronic liver disease
	chronic kidney disease (caution for CrCl < 30mL/min)
	valvular disease

Rivaroxaban may present risks during pregnancy. In view of the lack of studies [70], rivaroxaban should only be used by pregnant women after consultation with their healthcare provider. The identified drug interactions of rivaroxaban are recorded in Table IV.

Table IV

Drug interactions of rivaroxaban

Co-administered drug	Clinical consequences
Inducers of CYP450 and P-gp [47]	ineffectiveness
Inhibitors of CYP450 and P-gp [47]	increase bleeding risk
Antiarrhythmic drugs (dronedarone) [20]	increase bleeding risk
Antiplatelet and antithrombotic drugs [20]	increase bleeding time
Nonsteroidal anti-inflammatory drugs (NSAID's) [20]	Increase bleeding time

The anticoagulant effect of rivaroxaban is reversed by 4-factor prothrombin complex concentrate (4F-PCC) [23] and Andexanet alfa [52]. However, studies have shown that the use of Andexanet alfa is more effective than 4F-PCC and reduces in-hospital mortality by up to 50 % [12].

Physicochemical properties of rivaroxaban

Rivaroxaban is 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxo-morpholin-4- yl)phenyl]-1,3-oxazolidin-5-yl]methyl] thiophene-2-carboxamide. Its chemical formula is $C_{19}H_{18}ClN_3O_5S$ and it has a molecular wight of

435.9. Rivaroxaban is a white or yellowish powder [61]. It is included in class II by the Biopharmaceutics Classification System (BCS), meaning its dissolution is the rate-limiting step for absorption [43]. Its solubility in various solvents is presented in Table V.

Table V

The solubility of rivaroxaban

Solvent	Solubility
Water [61]	practically insoluble
aqueous media with pH 1 - 9 [18]	practically insoluble
dimethyl sulfoxide [61]	freely soluble
anhydrous ethanol [61]	practically insoluble
Heptane [61]	practically insoluble
Acetone [61]	slightly soluble
polyethylene glycol [18]	slightly soluble

Also, the partition coefficient in octanol/water ($logP_{O/W}$) is 1.5 [18]. Tests show that rivaroxaban crystallizes in three polymorphs, polymorph I being the thermodynamically stable one [18].

Identification methods [61] include IR spectrophotometry and enantiomeric purity, a test performed by liquid chromatography.

Methods for improving aqueous solubility of rivaroxaban

Rivaroxaban has been formulated in several ways to optimize its water solubility, in particular to increase bioavailability while maintaining a consistent efficacy and safety profile.

Functional groups like carbonyl and aromatic rings give rivaroxaban, a hydrophobic substance with limited aqueous solubility, its hydrophobicity and its tendency to interact with other molecules.

The hydrophobic effect induces the encapsulation of rivaroxaban in various systems, as the hydrophobic molecules attach to other hydrophobic surfaces to reduce their exposure to the surrounding aqueous environment.

Rivaroxaban is a neutral, nonionizable compound that is soluble at various pH values. Its mole fraction solubility in water was estimated by experimental observations at 298.15 K to be about 2.89×10^{-7} [40], and solubility studies in distilled water gave a comparable value of 3.02×10^{-7} [36].

Several approaches have been developed to improve the absorption and stability of the drug and minimize side effects, including the use of microspheres, liposomes, self-nanoemulsifying drug delivery systems (SNEDDS), solid lipid nanoparticles (SLN), cocrystals, sustained release and solid dispersion [5].

In addition, other studies have shown that the incorporation of rivaroxaban-hydroxypropyl-β cyclodextrin inclusion complexes into solid dosage forms helps to overcome the drug's solubility limitations and improve its bioavailability [56].

On the other hand, pulmonary delivery could be an alternative to achieve an immediate effect, and research [24] shows that spray drying enables the formulation of rivaroxaban particles suitable for this administration method.

Inclusion complexes with cyclodextrins

Kang JH *et al*. [36] achieved high water solubility of RIV by forming its complex with hydroxypropyl-beta-cyclodextrin and HPMC 2208, resulting in a 100% dissolution rate independent of pH and implicitly of the meal.

Meantime, Khan WH *et al*. [40] demonstrated that ternary inclusion systems formed by RIV with β-cyclodextrin and different hydrophilic polymers were superior to the binary combinations (RIV with β-cyclodextrin) in terms of enhancing the hydrophobic drug's solubility and dissolution.

In a recent study developed by our team, RIV was incorporated in an inclusion complex with hydroxypropyl-beta-cyclodextrin, at a minimal molar ratio of 1:1 in order to enhance the solubility and dissolution of RIV and avoid the use of surfactants such as sodium lauryl sulphate in the dosage formulation. The novelty of the study lies in utilizing liquid-state inclusion complexes in solid oral dosage forms, by spraying their dispersion onto the surface of cellulose pellets. The results proved that the contact area between RIV and gastrointestinal fluids is significantly increased, leading to improved release performance [56].

Development of eutectic mixtures

Studies have shown that the inclusion of rivaroxaban in a eutectic mixture could have advantages in terms of its bioavailability and thermal stability. For example, Shaligram PS *et al*. [63] investigated the eutectic mixture of rivaroxaban and mandelic acid (MA) and demonstrated a threefold drug release of the mixture compared to RIV alone. The amorphous solid dispersions were produced with a polymer matrix of hydrophilic polymers, in particular Kollidon® VA 64 and the plasticizer Kolliphor® P 188. In the hot melt extrusion method, the use of the eutectic RIV-MA (1:4) with a significantly lower melting point enhanced the solubility, dissolution rate and thermal stability.

Nanotechnology-based formulation

Whether it is the reduction of particle size, which increases the dissolution surface area, or the formation of nanoemulsions, these methods have been shown to be effective in improving the pharmacokinetic profile of RIV.

Mehnert W and Mäder K [50] stated that solid lipid nanoparticles (SLN) have the advantage that they consist of physiological components, are easy to produce, increase the bioavailability and stability of drugs and also offer many formulation possibilities.

Luo X *et al*. [46] included RIV in SLNs to improve its biopharmaceutical behavior and found that the SLNs can carry the RIV with increased therapeutic efficacy and without toxicity.

A recent study by Singh B *et al*. [64] has shown that self-emulsifying drug delivery systems (SEDDS) have overcome many of the problems caused by the reduced water solubility of drugs.

In addition, Xue X *et al*. [76] showed that the SEDDS formulation for RIV is an alternative to improve its bioavailability. The authors selected isopropyl myristate as the oily phase, Tween 80 as surfactant and 1,2-propanediol as co-surfactant. The initial composition of the SNEDDS formulation was optimized using the pseudo ternary phase diagram. The central composite design of the response surface methodology was used to select the optimal rivaroxaban SNEDDS formulation. According to the study's findings, the SNEDDS formulation can improve oral bioavailability and reduce the impact of food in the fasting state.

Co-crystallization

Co-crystals are multi-component systems that can lead to an improvement in physicochemical properties that are clinically significant [16]. For example, RIV co-crystals have been studied by Meng Y *et al*. [51] and they have shown that this type of formulation is suitable for increased absorbability and bioavailability. Five cocrystals were employed as cofomers: succinic acid (SA), nicotinamide (NA), isonicotinamide (IA), p-hydroxybenzoic acid (HBA), and 2,4-dihydroxy-benzoic acid (DBA). The solubility, dissolution (under sink conditions), and intrinsic dissolution rates of RIV-DBA and RIV-HBA cocrystals were clearly superior to those of RIV. Furthermore, in comparison to RIV, the in vitro permeability levels of RIV-DBA and RIV-IA cocrystals in a Caco-2 cell model were noticeably higher. Also, the bioavailability of RIV-DBA and RIV-HBA cocrystals was higher than that of RIV, according to pharmacokinetic experiments conducted on beagle dogs.

Liposomes

Considering their advantages in terms of improving drug's physicochemical properties, liposomes are one of the most commonly used drug carriers [3], which is also being investigated for RIV formulations. Liposomes have a variety of properties due to their lipidic composition, including stiffness, size, release rate, and surface charge [68].

Elsayad MK *et al*. [14] demonstrated the efficacy of the chitosan coated liposomes prepared in a liquid formulation to improve the oral bioavailability of RIV regardless of nutritional status. Classic liposomes (CLs) and flexible liposomes (FLs) coated with chitosan (CS) were prepared. Compared to a RIV suspension, the formulation containing PL S100/ Tween 80 (85/15 % w/w) and CS solution at a concentration of 0.2 % w/v increased the bioavailability of RIV in the fed and fasting states by 59.66 % and 26.97 %, respectively.

Rivaroxaban pharmaceutical dosage forms

According to data provided by the European Medicines Agency, rivaroxaban is available in film-coated tablets. Each tablet contains micronized rivaroxaban in varying doses, more precisely, levels of 2.5 mg, 10 mg, 15 mg and 20 mg. Furthermore, rivaroxaban is available as oral suspension, for paediatric use or people with dysphagia [17].

In order to achieve suitable *in vivo* performance, the choice of excipients is a key aspect. Various research studies have focused on the manufacturing of different pharmaceutical oral dosage forms containing rivaroxaban.

In the original product (Xarelto®), rivaroxaban was incorporated into the cores of immediate-release film-coated tablets using microcrystalline cellulose and lactose monohydrate as fillers, croscarmellose sodium as disintegrant, hypromellose as binder, sodium lauryl sulphate as wetting agent and magnesium stearate as lubricant [17].

Choi MJ *et al*. [9] successfully improved the bioavailability of rivaroxaban by encapsulating it in nanoparticles based on poly(lactic-co-glycolic acid), PLGA.

Formulated as solid dispersions, drugs have improved bioavailability, increased dissolution rate and prolonged absorption [2]. Shah PJ *et al*. demonstrated that the development of a solid dispersions of rivaroxaban by the fusion method using PEG 4000 as a carrier and neusilin as an adsorbent improves oral bioavailability [62]. In this case, rivaroxaban tablets based on its solid dispersions may be an efficient alternative solid dosage form.

Rivaroxaban-loaded microspheres offer significant clinical benefits by improving patient adherence to therapy by reducing the frequency of use [67]. Choi MJ *et al*. again demonstrated that rivaroxaban-loaded microspheres based on poly(vinylpyrrolidone) K30 as a carrier and SLS as a surfactant can improve the bioavailability, dissolution rate and solubility of rivaroxaban [9].

In our previous study, the coated cellets containing rivaroxaban, hydroxypropyl-beta-cyclodextrin and

hydroxypropyl-cellulose, were incorporated into hard gelatin capsules, which showed similar release profiles with a higher dissolution rate within the first 10 minutes compared to Xarelto® film-coated tablets [56].

Oral suspensions are mainly used for pediatric patients or people with swallowing disorders. However, studies by Abouhussein DMN *et al*. [1] have shown that the development of a liquid nano-sized drug delivery system has improved the bioavailability of rivaroxaban so that it can be used for emergencies.

In addition, the EMA has approved Xarelto 1 mg/mL granules for oral suspension containing microcrystalline cellulose as filler, hypromellose as thickener, acacia gum, xanthan gum and carmellose sodium as stabilizers, citric acid as pH adjuster, sodium benzoate as preservative and mannitol and maltodextrin as sweeteners [19].

Conclusions

The therapeutic benefits of rivaroxaban are generally recognised in the scientific community, but its oral bioavailability is limited by its low water solubility. Various studies have been conducted to improve the solubility of rivaroxaban, and they go in two directions. The first strategy aims to make changes to the chemical structure of rivaroxaban, mainly by incorporating it into different complexes. The second approach targets innovative formulations for new delivery systems. In this respect, the development of micro- and nanoparticles holds great potential for the future of rivaroxaban delivery. Extensive pharmaceutical research is still needed and new technologies should be developed to improve the oral bioavailability of rivaroxaban and thus its therapeutic efficacy.

Conflict of interest

The authors declare no conflict of interest.

References

1. Abouhussein DMN, Bahaa El Din Mahmoud D, Mohammad FE, Design of a liquid nano-sized drug delivery system with enhanced solubility of rivaroxaban for venous thromboembolism management in paediatric patients and emergency cases. *J Liposome Res.*, 2019; 29(4): 399-412.
2. Allawadi DS, Neelam S Sukhbir A, Sandeep A, Solid dispersions: a review on drug delivery system and solubility enhancement. *IJPSR*, 2013; 4(6): 2094-2105.
3. Almeida B, Nag OK, Rogers KE, Delehanty JB, Recent Progress in Bioconjugation Strategies for Liposome-Mediated Drug Delivery. *Molecules*, 2020; 25(23): 5672
4. Alquwaizani M, Buckley L, Adams C, Fanikos J, Anticoagulants: A Review of the Pharmacology, Dosing, and Complications. *Curr Emerg Hosp Med Rep.*, 2013; 1(2): 83-97
5. Al-shoubki AA, Teaima H, Abdelmonem M, El-nabarawi RMA, Elhabal SF, Bioavailability enhancement strategies for rivaroxaban: a noteworthy review. *Int J App Pharm.*, 2023; 15(6): 33-37
6. American Chemical Society, AstraZeneca, Sanofi Cut Programs. Chemical & Engineering News, 2013; 91(23): 17.
7. Ballestri S, Romagnoli E, Arioli D, Coluccio V, Marrazzo A, Athanasiou A, Di Girolamo M, Cappi C, Marietta M, Capitelli M, Risk and Management of Bleeding Complications with Direct Oral Anticoagulants in Patients with Atrial Fibrillation and Venous Thromboembolism: a Narrative Review. *Adv Ther.*, 2023; 40(1): 41-66
8. Bratsos S, Pharmacokinetic Properties of Rivaroxaban in Healthy Human Subjects. *Cureus*, 2019; 11(8): e5484
9. Choi MJ, Woo MR, Baek K, Park JH, Joung S, Choi YS, Choi HG, Jin SG, Enhanced Oral Bioavailability of Rivaroxaban-Loaded Microspheres by Optimizing the Polymer and Surfactant Based on Molecular Interaction Mechanisms. *Mol Pharm.*, 2023; 20(8): 4153-4164
10. Cruz Rodriguez JB, Okajima K, Greenberg BH, Management of left ventricular thrombus: a narrative review. *Ann Transl Med.*, 2021; 9(6): 520
11. Dobesh PP, Fermann GJ, Christoph MJ, Koch B, Lesén E, Chen H, Lovelace B, Dettling T, Danese M, Ulloa J, Danese S, Coleman CI, Lower mortality with Andexanet alfa *vs* 4-factor prothrombin complex concentrate for factor Xa inhibitor-related major bleeding in a U.S. hospital-based observational study. *Res Pract Thromb Haemost.*, 2023; 7(6): 102192
12. Dwyer J, Walsh C, First Time European Approval for Xarelto in ACS. Decision Resources, 2014; 19, available at: http://decisionresources.com.
13. Elenjickal EJ, Travlos CK, Marques P, Mavrakanas TA, Anticoagulation in Patients with Chronic Kidney Disease. *Am J Nephrol.*, 2024; 55(2): 146-164.
14. Elsayad MK, Mowafy HA, Zaky AA, Samy AM, Chitosan caged liposomes for improving oral bioavailability of rivaroxaban: *in vitro* and *in vivo* evaluation. *Pharm Dev Technol.*, 2021; 26(3): 316-327.
15. Eribaxaban, available at: www.adinsInsight.springer.com.
16. Essen CV, Luedeker D, *In silico* co-crystal design: Assessment of the latest advances. *Drug Discov Today*, 2023; 28(11): 103763.
17. European Medicines Agency, Xarelto: EPAR, Medicine overview, reference number: EMA/617633/2020, available at: www.ema.europa.eu.
18. European Medicines Agency, Xarelto: EPAR, Public assessment report, available at: www.ema.europa.eu.
19. European Medicines Agency, Xarelto, INN-rivaroxaban, available at: www.ema.europa.eu.
20. Ferri N, Colombo E, Tenconi M, Baldessin L, Corsini A, Drug-Drug Interactions of Direct Oral Anticoagulants (DOACs): From Pharmacological to Clinical Practice. *Pharmaceutics*, 2022; 14(6): 1120.
21. Fox BD, Kahn SR, Langleben D, Eisenberg MJ, Shimony A, Efficacy and safety of novel oral anticoagulants for treatment of acute venous thromboembolism: direct and adjusted indirect meta-

analysis of randomised controlled trials. *BMJ*, 2012; 345: e7498.
22. Franchini M, Mannucci PM, Association between venous and arterial thrombosis: clinical implications. *Eur J Intern Med.*, 2012; 23: 333-337
23. Giffard-Quillon L, Desmurs-Clavel H, Grange C, Jourdy Y, Dargaud Y, Reversal of rivaroxaban anticoagulant effect by prothrombin complex concentrates: which dose is sufficient to restore normal thrombin generation?. *Thromb J.*, 2020 ;18: 15.
24. Groß R., Kožák J, Chrétien C, Berkenfeld K, Pellequer Y, Lamprecht A, Fast onset of thrombolytic effect of efficiently inhalable spray-dried rivaroxaban powder formulations. *Int J Pharm.*, 2024; 667(Part A): 124912.
25. Grogan K, Astellas pulls the plug on darexaban. *Pharmatimes*, 2014, available: https://pharmatimes.com.
26. Grymonprez M, De Backer TL, Bertels X, Steurbaut S, Lahousse L, Long-term comparative effectiveness and safety of dabigatran, rivaroxaban, apixaban and edoxaban in patients with atrial fibrillation: A nationwide cohort study. *Front Pharmacol.*, 2023; 14: 1125576.
27. Gulseth MP, Michaud J, Nutescu EA, Rivaroxaban: an oral direct inhibitor of factor Xa. *Am J Health Syst Pharm.*, 2008; 65(16): 1520-1529.
28. Hauptmann J, Stürzebecher J, Synthetic Inhibitors of Thrombin and Factor Xa. *Thromb Res.*, 1999; 93: 203-241.
29. Heestermans M, Poenou G, Hamzeh-Cognasse H, Cognasse F, Bertoletti L, Anticoagulants: A Short History, Their Mechanism of Action, Pharmacology, and Indications. *Cells*, 2022; 11(20): 3214.
30. Hindley B, Lip GYH, McCloskey AP, Penson PE, Pharmacokinetics and pharmacodynamics of direct oral anticoagulants. *Expert Opin Drug Metab Toxicol.*, 2023; 19(12): 911-923.
31. Hirsh J, Dalen J, Anderson DR, Poller L, Bussey H, Ansell J, Deykin D, Oral Anticoagulants: Mechanism of Action, Clinical Effectiveness, and Optimal Therapeutic Range. *Chest*, 2001; 119: 8S-21S.
32. www.ema.europa.eu.
33. www.fda.gov.
34. Ingason AB, Hreinsson JP, Agustsson AS, Lund SH, Rumba E, Palsson DA, Reynisson IE, Gudmundsdottir BR, Onundarson PT, Bjornsson ES, Comparison of the effectiveness and safety of direct oral anticoagulants: a nationwide propensity score-weighted study. *Blood Adv.*, 2023; 7 (11): 2564-2572.
35. Jones A, Al-Horani RA, Venous Thromboembolism Prophylaxis in Major Orthopedic Surgeries and Factor XIa Inhibitors. *Med Sci.*, 2023; 11(3): 49
36. Kang JH, Lee JE, Jeong SJ, Park CW, Kim DW, Weon KY, Design and Optimization of Rivaroxaban-Cyclodextrin-Polymer Triple Complex Formulation with Improved Solubility. *Drug Des Devel Ther.*, 2022; 16: 4279-4289.
37. Kearon C, Dose-response study of recombinant human soluble thrombomodulin (ART-123) in the prevention of venous thromboembolism after total hip replacement. *J Thromb Haemost.*, 2005; 3: 962-968.
38. Key NS, Khorana AA, Kuderer NM, Bohlke K, Lee AYY, Arcelus JI, Wong SL, Balaban EP, Flowers CR, Francis CW, Gates LE, Kakkar AK, Levine MN, Liebman HA, Tempero MA, Lyman GH, Falanga A, Venous Thromboembolism Prophylaxis and Treatment in Patients With Cancer: ASCO Clinical Practice Guideline Update. *J Clin Oncol.*, 2020; 38(5): 496-520.
39. Khan F, Tritschler T, Kahn SR, Rodger MA, Venous thromboembolism. *Lancet*, 2021; 398(10294): 64-77.
40. Khan WH, Asghar S, Khan IU, Irfan M, Alshammari A, Rajoka MSR, Munir R, Shah PA, Khalid I, Razzaq FA, Khalid SH, Effect of hydrophilic polymers on the solubility and dissolution enhancement of rivaroxaban/beta-cyclodextrin inclusion complexes. *Heliyon*, 2023; 9(9): e19658.
41. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G, Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. *Clin Pharmacol Ther.*, 2005; 78(4): 412-421.
42. Kubitza D, Becka M, Mueck W, Zuehlsdorf M, The Effect of Extreme Age, and Gender, on the Pharmacology and Tolerability of Rivaroxaban - An Oral, Direct Factor Xa Inhibitor. *Blood*, 2006; 108(11): 905.
43. Kushwah V, Arora S, Tamás Katona M, Modhave D, Fröhlich E, Paudel A, On Absorption Modeling and Food Effect Prediction of Rivaroxaban, a BCS II Drug Orally Administered as an Immediate-Release Tablet. *Pharmaceutics*, 2021; 13(2): 283.
44. Kvasnicka T, Malikova I, Zenahlikova Z, Kettnerova K, Brzezkova R, Zima T, Ulrych J, Briza J, Netuka I, Kvasnicka J, Rivaroxaban - Metabolism, Pharmacologic Properties and Drug Interactions. *Curr Drug Metab.*, 2017; 18(7): 636-642.
45. Liu XQ, Li ZR, Wang CY, Chen YT, Jiao Z, Is a Lower Dose of Rivaroxaban Required for Asians? A Systematic Review of a Population Pharmacokinetics and Pharmacodynamics Analysis of Rivaroxaban. *Pharmaceutics*, 2023; 15(2): 588.
46. Luo X, Saleem A, Shafique U, Sarwar S, Ullah K, Imran M, Zeb A, Din FU, Rivaroxaban-loaded SLNs with treatment potential of deep vein thrombosis: in-vitro, in-vivo, and toxicity evaluation. *Pharm Dev Technol.*, 2023; 28(7): 625-637.
47. Mar PL, Gopinathannair R, Gengler BE, Chung MK, Perez A, Dukes J, Ezekowitz MD, Lakkireddy D, Lip GYH, Miletello M, Noseworthy PA, Reiffel J, Tisdale JE, Olshansky B; from the American Heart Association Electrocardiography & Arrhythmias Committee of the Council of Clinical Cardiology, Drug Interactions Affecting Oral Anticoagulant Use. *Circ Arrhythm Electrophysiol.*, 2022; 15(6): e007956.
48. Mavrakanas T, Bounameaux H, The potential role of new oral anticoagulants in the prevention and treatment of thromboembolism. *Pharmacol Ther.*, 2011; 130: 46-58.
49. Mega JL, Braunwald E, Wiviott SD, Bassand JP, Bhatt DL, Bode C, Burton P, Cohen M, Cook-Bruns N, Fox KA, Goto S, Murphy SA, Plotnikov AN, Schneider D, Sun X, Verheugt FW, Gibson CM, Rivaroxaban in patients with a recent acute coronary syndrome. *N Engl J Med.*, 2012; 366(1): 9-19.
50. Mehnert W, Mäder K, Solid lipid nanoparticles: production, characterization and applications. *Adv Drug Deliv Rev.*, 2001; 47(2-3): 165-196.

51. Meng Y, Tan F, Yao J, Cui Y, Feng V, Li Z, Wang Y, Yang Y, Gong W, Yang M, Kong X, Chunsheng Gao, Preparation, characterization, and pharmacokinetics of rivaroxaban cocrystals with enhanced in vitro and in vivo properties in beagle dogs. *Int J Pharm.*, 2022; 4(X): 100119.
52. Milling TJ Jr, Middeldorp S, Xu L, Koch B, Demchuk A, Eikelboom JW, Verhamme P, Cohen AT, Beyer-Westendorf J, Gibson CM, Lopez-Sendon J, Crowther M, Shoamanesh A, Coppens M, Schmidt J, Albaladejo P, Connolly SJ, Final Study Report of Andexanet Alfa for Major Bleeding With Factor Xa Inhibitors. *Circulation*, 2023; 147(13): 1026-1038.
53. Morris TA, New Synthetic Antithrombotic Agents for Venous Thromboembolism: Pentasaccharides, Direct Thrombin Inhibitors, Direct Xa Inhibitors. *Clin Chest Med.*, 2010; 31(4): 707-718.
54. Mueck W, Agnelli G, Buller H, Rivaroxaban Has Predictable Pharmacokinetics (PK) and Pharmacodynamics (PD) When Given Once or Twice Daily for the Treatment of Acute, Proximal Deep Vein Thrombosis (DVT). *Blood*, 2007; 110 (11): 1880
55. Olie RH, Winckers K, Rocca B, Ten Cate H, Oral Anticoagulants Beyond Warfarin. *Annu Rev Pharmacol Toxicol.*, 2024; 64: 551-575.
56. Ozon EA, Mati E, Karampelas O, Anuta V, Sarbu I, Musuc AM, Mitran RA, Culita DC, Atkinson I, Anastasescu M, Lupuliasa D, Mitu MA, The development of an innovative method to improve the dissolution performance of rivaroxaban. *Heliyon*, 2024; 10(12): e33162.
57. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med.*, 2011; 365(10): 883-891.
58. Perzborn E, Roehrig S, Straub A, Kubitza D, Misselwitz F, The discovery and development of rivaroxaban, an oral, direct factor Xa inhibitor. *Nat Rev Drug Discov.*, 2011; 10: 61-75.
59. Perzborn E, Roehrig S, Straub A, Kubitza D, Mueck W, Laux V, Rivaroxaban: a new oral factor Xa inhibitor. *Arterioscler Thromb Vasc Biol.*, 2010; 30(3): 376-381.
60. Proietti M, Romanazzi I, Romiti GF, Farcomeni A, Lip GYH, Real-World Use of Apixaban for Stroke Prevention in Atrial Fibrillation: A Systematic Review and Meta-Analysis. *Stroke*, 2018; 49(1): 98-106.
61. Rivaroxaban Tablets. United States Pharmacopeia (2024). *USP Monographs, Rivaroxaban Tablets*. USP-NF. Rockville, MD: United States Pharmacopeia.
62. Shah PJ, Patel MP, Shah J, Nair AB, Kotta S, Vyas B, Amalgamation of solid dispersion and melt adsorption techniques for augmentation of oral bioavailability of novel anticoagulant rivaroxaban. *Drug Deliv Transl Res.*, 2022; 12(12): 3029-3046.
63. Shaligram PS, Pawar R, Shet N, Gonnade RG, A novel solid formulation of a rivaroxaban eutectic using a hot melt extruder with improved thermal stability and dissolution profile. *RSC Pharmaceutics*, 2024; 2: 114-123.
64. Singh B, Beg S, Khurana RK, Sandhu PS, Kaur R, Katare OP, Recent advances in self-emulsifying drug delivery systems (SEDDS). *Crit Rev Ther Drug Carrier Syst.*, 2014; 31(2): 121-185.
65. Singh AK, Noronha V, Gupta A, Singh D, Singh P, Singh A, Rivaroxaban: Drug review. *Cancer Res Stat Treat.*, 2020; 3 (2): 264-269
66. Streiff MB, Agnelli G, Connors JM, Crowther M, Eichinger S, Lopes R, McBane RD, Moll S, Ansell J, Guidance for the treatment of deep vein thrombosis and pulmonary embolism. *J Thromb Thrombolysis*, 2016; 41(1): 32-67.
67. Tan C, Xiong S, Preparation, Characterization and *in vitro/vivo* Evaluation of Long-Acting Rivaroxaban-Loaded Microspheres. *Curr Drug Deliv.*, 2023; 20(10): 1547-1558.
68. Toma I, Raduly L, Porfire A, Tefas LR, Zanoaga O, Berindan-Neagoe I, Tomuta I, Vinorelbine-loaded pH-sensitive liposomes: development, characterization and *in vitro* evaluation, *Farmacia*, 2024, 72(5): 1162-1170.
69. Upreti P, Gongati SR, Pandey N, Saad M, Vittorio T, Exploring the Causal Relationship Between Arterial and Venous Thromboembolism: A Case Series With Review of Literature. *Cureus*, 2023; 15(4): e37660.
70. Vauzelle C, [Direct oral anticoagulants and pregnancy]. *Gynecol Obstet Fertil Senol.*, 2021; 49(4): 301-303.
71. Weitz JI, New oral anticoagulants: a view from the laboratory. *Am J Hematol.*, 2012; 87(Suppl 1): S133-136.
72. Weitz JI, Jaffer IH, Fredenburgh JC, Recent advances in the treatment of venous thromboembolism in the era of the direct oral anticoagulants. *F1000Research.*, 2017; 6: 985.
73. *World Health Organization*, World Health Organization model list of essential medicines: 23nd list. Geneva: World Health Organization, 2023, available at: www.who.int.
74. Wu J, Wu J, Tang B, Wang X, Wei F, Zhang Y, Li L, Li H, Wang B, Wu W, Hong X, Suspected adverse drug reactions of rivaroxaban reported in the United States food and drug administration adverse event reporting system database: a pharmacovigilance study. *Front Pharmacol.*, 2024; 15: 1399172.
75. Xu K, Li H, Yang X, Zhang Y, Guangrong Y, Zhang G, Yan J, Peng J, Lu T, Effect of low molecular weight heparin in the prevention of severe pneumonia complicated with lower extremity deep vein thrombosis. *Farmacia*, 2024; 72(2): 294-297.
76. Xue X, Cao M, Ren L, Qian Y, Chen G, Preparation and Optimization of Rivaroxaban by Self-Nanoemulsifying Drug Delivery System (SNEDDS) for Enhanced Oral Bioavailability and No Food Effect. *AAPS PharmSciTech.*, 2018; 19(4): 1847-1859.
77. Zeng Y, Wang M, Low molecular weight heparin in the protection of parathyroid function after thyroid surgery. *Farmacia*, 2024, 72(6): 1317-1324.