UNIVERSITY OF MEDICINE AND PHARMACY "CAROL DAVILA"-

BUCHAREST

DOCTORAL SCHOOL

PHARMACY FIELD

STUDIES REGARDING THE MANUFACTURING AND EVALUATION OF SOME INNOVATIVE PHARMACEUTICAL SYSTEMS FOR ENSURING AN OPTIMAL RELEASE OF RIVAROXABAN FROM TABLETS

Summary of PhD Thesis

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2025

TABLE OF CONTENTS

LIST OF PUBLISHED SCIENTIFIC ARTICLES

Full-length articles published in ISI Thomson Reuters listed journals

1. **Solomon C.**, Niță D.T., Ozon E.A., Fița A.C., Viziteu H.M., Musuc A.M., Sârbu I., Mitu M.A. An overview of the pharmaceutical profile of rivaroxaban. Farmacia, 2025; 73 (1): 1-8, IF 1,6, https://farmaciajournal.com/wp-content/uploads/art-01-Solomon_Ozon_Mitu_1-8.pdf; https://doi.org/10.31925/farmacia.2025.1.1 (Capitolul 2 – pag. 13-23)
2. **Solomon C.**, Anuța V., Sârbu I., Ozon E.A., Musuc A.M., Bratan V., Rusu A., Surdu V.A., Croitoru C., Chandak A., Gavriloaia R.M., Balaci T.D., Niță D.T., Mitu M.A. Enhancing the Drug Release and Physicochemical Properties of Rivaroxaban via Cyclodextrin Complexation: A Comprehensive Analytical Approach. Pharmaceuticals MDPI, 2025; 18, IF 4,3, https://www.mdpi.com/1424-8247/18/6/761; https://doi.org/10.3390/ph18060761; (Capitolul 4 – pag. 44-55; Capitolul Capitolul 5 – pag. 56-79; Capitolul 6 – pag. 80-92; Capitolul 7 – pag. 93-105).
3. **Solomon C.,** Sârbu I., Anuța V., Ozon E.A., Musuc A.M., Fița A.C., Mitu M.A. Preformulation studies of tablets containing rivaroxaban – niacinamide cocrystallization compounds. Farmacia, 2025; 73 (3): 1-7, IF 1,6, https://doi.org/10.31925/farmacia.2025.3.17 (Capitolul 4 – pag. 48-50; Capitolul 6 – pag. 80-91).

INTRODUCTION

Rivaroxaban (RIV), a widely used direct oral anticoagulant (DOAC) and direct factor Xa inhibitor, is effective in the prevention and treatment of thromboembolic disorders, being frequently used in the treatment and prevention of venous thromboembolism, stroke in atrial fibrillation, and other thrombotic conditions [1,2]. However, its relatively low solubility in aqueous media limits its absorption from the gastrointestinal tract, leading to unpredictable bioavailability and variable therapeutic performance, and for this reason, it is classified as a class II drug in the Biopharmaceutical Classification System (BCS) [3,4].

Therefore, increasing the solubility of rivaroxaban is essential to optimize its therapeutic efficacy and ensure adequate bioavailability.

The main objective of the doctoral thesis is to increase the solubility of rivaroxaban by incorporating it into new compounds identified and characterized using modern technologies, followed by their inclusion using the direct compression process into rapid-release tablets.

In the first part of the study, we aimed to include RIV in the cavity of different beta-cyclodextrins to increase the solubility of rivaroxaban and increase its incorporation capacity into fast-release tablets without the need to add synthetic surfactants. To complex RIV, we selected three different beta-cyclodextrins: β-cyclodextrin (β-CD), hydroxypropyl-β-cyclodextrin (HP-β-CD) and methyl-β-cyclodextrin (Me-β-CD), due to the fact that the molecular dimensions of the active ingredient are suitable for encapsulation in their cavity, being able to form inclusion complexes, while the cavity of γ-cyclodextrins is too large, and that of α-cyclodextrins is too small and cannot create stable complexes with it.

This study aims to evaluate the potential of several cyclodextrin derivatives, such as β-cyclodextrin (β-CD), methyl-β-cyclodextrin (Me-β-CD) and hydroxypropyl-β-cyclodextrin (HP-β-CD), in improving the solubility and dissolution profile of rivaroxaban by forming inclusion complexes through the lyophilization technique. The aim of the present research is to investigate the physicochemical properties of these three inclusion complexes using different and complementary analytical techniques, including Fourier transform infrared spectroscopy (FTIR), scanning electron microscopy (SEM), X-ray diffraction (XRD) and thermogravimetric analysis (TGA). These techniques provide information on the molecular interactions, structural changes and stability of the obtained inclusion complexes. The novelty of this study lies in the comprehensive comparison of several cyclodextrin derivatives in the formulation of rivaroxaban

inclusion complexes. By exploring how each cyclodextrin derivative influences the solubility, dissolution rate and stability of rivaroxaban, the study provides a more detailed understanding of their potential in drug formulation.

In the second part of the study, we aimed to synthesize and characterize rivaroxaban-niacinamide cocrystals prepared in two different molar ratios (1:1 and 1:2 molar ratios).

Pharmaceutical cocrystals are supramolecular crystalline solids composed of an active pharmaceutical ingredient and a pharmaceutically acceptable neutral former [5] or a coformer [6], both of which are solid at ambient temperature [7].

Among various coformers, niacinamide (NIA) or pyridine-3-carboxamide (a water-soluble form of vitamin B3), also known as nicotinamide, is commonly used as a pharmaceutical coformer due to its excellent safety profile, biocompatibility, strong hydrogen bond donor/acceptor capacity, low molecular weight, and ability to improve pharmacokinetic profiles and increased water solubility of coformulated drugs compared to the active ingredient alone [8,9].

Two types of RIV-NIA cocrystals were prepared by varying the molar ratio between the two components. By investigating the structural, thermal, and morphological properties of the resulting cocrystals, it was evaluated how the molar ratio influences the nature of the solid forms and their potential pharmaceutical advantages. Advanced analytical techniques, including FT-IR spectroscopy, scanning electron microscopy (SEM), X-ray powder diffraction (XRD) and thermal analysis (TG-DTA), were used to elucidate the physicochemical profile of each cocrystal system. The novelty of this research lies in the comparative investigation of two different molar ratios (1:1 and 1:2) of rivaroxaban and niacinamide to form pharmaceutical cocrystals. The objective of this study is to design, synthesize and characterize rivaroxaban-niacinamide cocrystals at molar ratios of 1:1 and 1:2 using the “solvent evaporation” method.

In the preformulation studies, all the obtained compounds, as well as the powders for direct compression, were analyzed for pharmacotechnical properties such as particle size, moisture content, flow, bulk and tamped densities and compressibility index.

Using the direct compression process, ten different batches of tablets were obtained and subjected to quantitative and qualitative control. Finally, in vitro dissolution studies were performed in two different simulated gastrointestinal environments to compare the dissolution

profiles of the tablets obtained with pure rivaroxaban and with the original commercial product existing on the pharmaceutical market.

I. GENERAL PART

1. Pharmaceutical profile of rivaroxaban

1.1.Therapeutic context of rivaroxaban

Rivaroxaban (RIV) is the first direct, non-cofactor-dependent, specific factor Xa inhibitor approved as a drug for human use [10].

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 [11]. 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 after elective hip or knee replacement. It was first approved by the FDA in 2011, so it was not available as a generic drug until 2024 [12]. Due to its effectiveness and popularity, it is included in the World Health Organization's List of Essential Medicines [13].

1.2.Pharmacological profile

Rivaroxaban is a direct oral anticoagulant (DOAC) [14]. In addition, rivaroxaban is an oral, direct, reversible, competitive, rapid and dose-dependent inhibitor of factor Xa [15]. Given its mechanism of action, rivaroxaban therefore causes inhibition of thrombin generation and prolongation of prothrombin time [16].

Due to its predictable pharmacokinetics and pharmacodynamics, the pharmacological effect of rivaroxaban is closely related to plasma concentrations in healthy volunteers [17], therefore rivaroxaban is an effective, well-tolerated [18], safe and specific inhibitor of factor Xa.

1.3.Physicochemical properties of rivaroxaban

Rivaroxaban is 5-chloro-N-[[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl]methyl]thiophene-2-carboxamide. Its chemical formula is C19H18ClN3O5S and its molecular weight is 435.9. Rivaroxaban is a white to yellowish powder [19]. It is classified as class II according to the Biopharmaceutical Classification System (BCS), which means that its dissolution is the rate-limiting step in absorption [20].

1.4.Methods for improving the water solubility of rivaroxaban

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

Functional groups such as carbonyl and aromatic rings confer on rivaroxaban, a hydrophobic substance with limited aqueous solubility, its hydrophobicity and its tendency to interact with other molecules [21].

1.5.Pharmaceutical dosage forms for rivaroxaban

According to the European Medicines Agency, rivaroxaban is available in the form of film-coated tablets. Each tablet contains micronized rivaroxaban in varying dosages, namely 2.5 mg, 10 mg, 15 mg and 20 mg. In addition, rivaroxaban is available as an oral suspension, for pediatric use or for people with dysphagia [22].

To achieve adequate in vivo performance, the choice of excipients is crucial. Various research studies have focused on the manufacture of different oral dosage forms containing rivaroxaban.

2. Techniques for bringing into solution medicinal substances that are poorly or poorly soluble in water

Increasing the solubility and bioavailability of poorly water-soluble active pharmaceutical ingredients (APIs) is crucial for drug development, whether innovative or generic. This improvement is vital to guarantee the efficacy and safety of treatments, as well as to optimize how the API is released, absorbed and exerts its pharmacological effects..

3. PERSONAL CONTRIBUTIONS REGARDING THE OBTAINING AND EVALUATION OF INNOVATIVE PHARMACEUTICAL SYSTEMS TO ENSURE OPTIMAL RELEASE OF RIVAROXABAN FROM TABLETS

3. Working hypothesis and general objectives

The study of the doctoral thesis is based on the use of two different technologies known to induce an increase in the water solubility of poorly soluble substances, applied to rivaroxaban.

- The first method is based on the incorporation of rivaroxaban into the cavity of three beta-cyclodextrins (β-CD, Me-β-CD and HP-β-CD) in a molar ratio of 1:1.
- The second method is based on the formation of co-crystals of rivaroxaban with niacinamide in two different molar ratios (1:1 and 1:2).

The general objectives pursued were:

1. Obtaining inclusion compounds of rivaroxaban in β-CD, Me-β-CD and HP-β-CD, in a molar ratio of 1:1

2. Obtaining cocrystals of rivaroxaban with niacinamide in two different molar ratios 1:1 and 1:2

3. Identification and physicochemical and pharmacotechnical characterization of inclusion compounds and cocrystals

4. Preformulation studies of tablets containing all synthesized compounds

5. Formulation and manufacture of tablets using the direct compression method

6. Qualitative and quantitative control of the obtained tablets

7. Evaluation of the in vitro release performance of rivaroxaban from all prepared tablets, in two biorelevant simulation environments and comparison with the commercial product available on the pharmaceutical market.

4. General research methodology

4.1. Materials

Labormed-Pharma SA donated micronized RIV (Form I) produced by Neuland Laboratories Limited, and Fagron, Greece, donated niacinamide (NIA). Global Holding Group Co., Ltd. (Ningbo, China) provided the three cyclodextrins (β-CD, HP-β-CD and Me-β-CD), and Avicel® PH 102 was purchased from International Flavors and Fragrances Inc. IFF, USA, and Flowlac® 100 was supplied by Meggle GmbH & Co. KG, Germany. EXPLOTAB® is produced by JRS PHARMA GmbH & Co. KG, Rosenberg, Germany, and LIGAMED® MF-2-V by Peter Graven NV, Netherlands.

4.2.Solubility studies

Based on the Higuchi and Connors phase-solubility diagrams [23], the apparent stability constant (Kst) was calculated assuming the formation of a 1:1 stoichiometric inclusion complex, using the following equation:

$$K_{st} = \frac{\text{panta}}{S_0\,(1 - \text{panta})} \quad (1)$$

Where :

- K_{st} = apparent stability constant of the inclusion complex formed in a molar ratio of 1 : 1;
- S_0 = intrinsic solubility of rivaroxaban in the absence of CD.

4.3.Obtaining and characterizing binary systems

4.3.1. Preparation of RIVA-CD compounds

Six different binary systems were prepared, maintaining the same 1:1 molar ratio between RIV and CD. Three of these were inclusion complexes of RIV in the β-CD, HP-β-CD and Me-β-CD cavities, and the other three were simple physical mixtures that served as references for the characterization studies of the guest-host compounds.

4.3.2. Preparation of RIV-NIA systems

Four different systems were prepared: two were cocrystals formed by RIV with NIA in two different molar ratios of 1:1 and 1:2 (RIV:NIA), and two were simple physical mixtures used as reference samples for cocrystal characterization studies.

4.3.3. Infrared spectroscopic measurements (FT-IR)

Infrared spectroscopic (FTIR) measurements were performed using a NICOLET 6700 FT-IR spectrophotometer (Thermo Electron Corporation), using Fourier transform infrared spectroscopy (FT-IR), in transmission mode. Spectra were collected in the range 4000–400 cm^{-1}, using a resolution of 4 cm^{-1}.

4.3.4. Thermal analysis

Thermal analysis was performed using a NETZSCH STA 449 F3 Jupiter instrument (Selb, Germany), over a temperature range of 25–600°C.

4.3.5. X-ray diffraction

Room temperature X-ray diffraction (XRD) measurements were performed on a Bruker D8 Advance diffractometer using Ni-filtered Cu-Kα radiation (λ = 1.5418 Å). The X-ray tube was operated at 40 kV and 40 mA.

4.3.6. Morphological analysis (SEM)

Morphological analysis (SEM) of the starting materials and the resulting compounds was performed using a Tescan Vega LMU scanning electron microscope (Brno, Czech Republic), operated in low vacuum mode (20 Pa) at an accelerating voltage of 10 kV.

4.4.Preformulation studies of the tablets based on rivaroxaban compounds

4.4.1. Formulation of powders for direct compression

The amounts of each ingredient were calculated to obtain tablets with a total mass of 200 mg, corresponding to a concentration of 10 mg RIV. Ten series of compound powders were prepared, three of which contained inclusion complexes as active ingredients, three simple physical mixtures of RIV and the three CDs, two contained co-crystallization compounds of RIV and NIA in different molar ratios (1:1 and 1:2), while the last two contained simple physical mixtures of RIV and NIA. Table 1. presents the formulations that were selected for each binary system.

Table 1. – Compound powder formulations for direct compression

Ingredient	***Formulation/ Quantity (%)***									
	F1	**F2**	**F3**	**F4**	**F5**	**F6**	**F7**	**F8**	**F9**	**F10**
RIV-β-CD (lyophilized inclusion complex)	18	-	-	-	-	-	-	-	-	-
RIV-β-CD (physical mixture)	-	18	-	-	-	-	-	-	-	-
RIV-HP-β-CD (lyophilized inclusion complex)	-	-	22,50	-	-	-	-	-	-	-
RIV-HP-β-CD (physical mixture)	-	-	-	22,50	-	-	-	-	-	-
RIV-Me-β-CD (lyophilized inclusion complex)	-	-	-	-	20	-	-	-	-	-
RIV-Me-β-CD (physical mixture)	-	-	-	-	-	20	-	-	-	-
RIV-NIA (1:1 co-crystallization compound)	-	-	-	-	-	-	6,5	-	-	-
RIV-NIA (1:1 physical mixture)	-	-	-	-	-	-	-	6,5	-	-

RIV-NIA (1:2 co-crystallization compound)	-	-	-	-	-	-	-	-	8	-
RIV-NIA (1:2 physical mixture)	-	-	-	-	-	-	-	-	-	8
Avicel® PH 102	40	40	37,75	37,75	39	39	45,75	45,75	45	45
Flowlac® 100	40	40	37,75	37,75	39	39	45,75	45,75	45	45
EXPLOTAB®	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00
LIGAMED® MF-2-V	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00	1,00

4.4.2. Preparation of mixtures for direct compression

In a CMP 12 Plexiglas cube mixer from Pharmag GmbH, Klipphausen, Germany, all ingredients (except magnesium stearate) were mixed at a speed of 30 rpm for 20 minutes at room temperature. Finally, magnesium stearate was added under the same conditions and mixed for another two minutes.

4.4.3. Pharmacotechnical analysis of composed powders

All analyses were performed for all binary systems (inclusion complexes, co-crystallization compounds and physical mixtures) and for all materials for direct compression. Particle size, moisture content, flow and compressibility were analyzed.

4.5.Development and manufacture of tablets

4.5.1. Rivaroxaban tablet formulation

Based on the results of preformulation studies, all ten materials designed for direct compression exhibited pharmacotechnical properties suitable for processing into tablets.

4.5.2. Manufacturing of rivaroxaban tablets

In a single-station eccentric tablet press, Erweka EP-1 from Erweka, Germany, the previously obtained materials were compressed with different compression forces as required (5 kN for F1, F4-F6; 9 kN for F2; 6 kN for F3 and F8; 10 kN for F7 and F9, and 8.5 kN for F10).

4.6.Quality control of the obtained tablets

Quality control focused on organoleptic control, dimensions (height and diameter), mass uniformity, hardness, friability and disintegration time.

4.7.*In vitro* release

The release profiles for rivaroxaban 10 mg tablets were evaluated using a Vi-sion G2 Classic 6 dissolution tester (Teledyne Hanson, Chatsworth, CA, USA) configured with the USP II apparatus (paddles). Dissolutions were performed at 37.0 ± 0.5 °C and 75 rpm, in accordance with the USP guidelines for rivaroxaban tablets [192]. Each vessel contained 900 ml of dissolution medium, and two different media were evaluated: 0.022 M sodium acetate buffer at pH 4.5 containing 0.2% sodium dodecyl sulfate (the recommended compendial medium for rivaroxaban 10 mg tablets) and a 0.05 M phosphate buffer at pH 6.8 without surfactants.

4.8.HPLC analysis

Quantitative determination of rivaroxaban followed a validated reversed-phase HPLC procedure, adapted from a previously reported method [24].

5. Physico-chemical characterization of the prepared binary systems

5.1. Solubility studies

Based on the classification established by Higuchi and Connors, the phase-solubility diagrams obtained for the rivaroxaban–β-CD, rivaroxaban–Me-β-CD and rivaroxaban–HP-β-CD systems showed an AL-type profile for all three compounds, indicating the formation of water-soluble inclusion complexes. The AL-type diagrams are characterized by a linear increase in the apparent solubility of the active pharmaceutical ingredient with increasing cyclodextrin concentration over the entire range studied.

5.2.FT-IR analysis

The disappearance or significant reduction of the characteristic bands of rivaroxaban in the FTIR spectra of the RIV-β-CD, RIV-Me-β-CD and RIV-HP-β-CD complexes obtained by the lyophilization method suggests strong interactions between rivaroxaban and the cyclodextrin compounds, indicating a possible complexation by inclusion of the drug in the cyclodextrin cavity.

The shifts of the wavenumber positions towards the high wavenumber area for RIV and the low wavenumber area for NIA indicate that the new molecular interactions of RIV-NIA significantly influence the positions of the functional group, due to the intermolecular interactions of each cocrystal.

5.3.X ray diffraction

The absence of characteristic diffraction peaks of rivaroxaban in the XRD pattern indicates a strong interaction between the drug and the cyclodextrins, supporting the formation of an inclusion complex, as confirmed by FTIR analysis.

The XRD patterns of the two RIV-NIA cocrystals exhibit characteristic peaks with reduced intensity, clearly showing a distinctive pattern obtained by the simple superposition of the two starting materials, indicating the formation of a new solid crystalline phase.

5.4.SEM analysis

The SEM image of the inclusion complexes obtained by lyophilization reveals an amorphous morphology indicating the formation of a new solid phase, for all complexes.

The morphologies of both RIV-NIA cocrystals (molar ratios 1:1 and 1:2) were completely different from those of RIV and NIA, which further indicated that the obtained co-crystallization compounds had a new crystalline state under the effect of the solvent evaporation method.

5.5.Thermal analysis

The disappearance of the melting point of rivaroxaban in all three inclusion complexes suggests the formation of a new phase.

The shift of endothermic events in co-crystallization compounds is a thermodynamic property of them, indicating that RIV-NIA should be in a new solid crystalline phase instead of a mixture.

6. Preformulation studies of the tablets based on rivaroxaban compounds

6.1.Determination of particle size

Regarding the inclusion compounds, all of them showed a higher percentage of particles with a size of 125-160 μm, while in the physical mixtures, the majority of the particles were in the 160-250 μm particle size class. For F1-F6, a significant change in the particle size distribution can be observed compared to the binary systems, with a significant increase in the particle size. In these cases, particles larger than 250 μm were observed.

Comparing the RIV-NIA co-crystallization compounds with the RIV-NIA physical mixtures, the widths of the distributions are quite similar, with the majority of the particles having a diameter within the 125-250 μm fraction. Among the directly compressible materials, formulations containing RIV-NIA in a molar ratio of 1:1 had the highest fraction of coarse particles in the range of 160-250 μm (73.19% for F1 and 74.52% for F8).

6.2.Pharmacotechnical characteristics of powders

The pharmacotechnical characteristics of the RIV-CD-based samples are presented in Table 2.

Table 2.- Pharmacotechnical parameters of the RIV-CD-based samples

Formulation	*Parameter*							
	Moisture content (%)	*Flowing time (sec)*	*Angle of repose (θ grade)*	*Flowing rate (g/s)*	*Bulk density (g/ml)*	*Tapped density (g/ml)*	*Carr index (CI) (%)*	*Hausner ratio (HR)*
RIV-β-CD (inclusion complex)	4,03 ± 0,94	-*	-*	-*	0,258	0,427	39,57	1,65
RIV-β-CD (physical mixture)	2,14 ± 0,55	23,8 ± 0,27*	36,14 ± 2,45*	2,521*	0,385	0,520	25,96	1,35
RIV-HP-β-CD (inclusion complex)	4,25 ± 0,79	-*	-*	-*	0,233	0,375	37,86	1,60
RIV-HP-β-CD (physical mixture)	2,63 ± 0,81	24,6 ± 0,38*	37,27 ± 2,16*	2,439*	0,341	0,498	31,52	1,46
RIV-Me-β-CD (inclusion complex)	4,78 ± 0,83	-*	-*	-*	0,222	0,384	42,18	1,72
RIV-Me-β-CD (physical mixture)	2,97 ± 0,66	28,4 ± 0,15*	39,09 ± 2,75*	2,112*	0,316	0,463	31,74	1,47
F1	1,86 ± 0,43	17,2 ± 0,25**	29,11 ± 1,86**	3,488**	0,461	0,577	20,10	1,25
F2	1,47 ± 0,52	16,9 ± 0,47**	28,82 ± 1,39**	3,550**	0,554	0,681	18,64	1,22
F3	2,39 ± 0,88	15,4 ± 0,28**	27,66 ± 1,02**	3,896**	0,453	0,542	16,42	1,19
F4	1,98 ± 0,84	14,8 ± 0,31**	27,08 ± 0,84**	4,054**	0,446	0,521	14,39	1,16
F5	2,61 ± 0,76	18,8 ± 0,23**	30,15 ± 2,28**	3,191**	0,457	0,596	23,32	1,30
F6	2,14 ± 0,65	18,1 ± 0,44**	29,79 ± 2,12**	3,314**	0,494	0,617	19,93	1,24

*Stirring: 25 rpm, Nozzle: 25 mm

**No stirring, Nozzle: 15 mm

As expected, the inclusion complexes obtained by lyophilization contained the highest amount of moisture, ranging from 4.03% for the RIV-β-CD inclusion complex to 4.78% for the RIV-MeβCD inclusion complex.

All six powder formulations for direct compression demonstrated a much improved flow performance, all flowing through the 15 mm nozzle without the need for agitation. However, none of the samples has excellent flow behavior according to the European Pharmacopoeia criteria [25], but all have adequate flow behavior for the direct compression process.

According to the European Pharmacopoeia specifications, only F4, containing the physical mixture RIV-HP-β-CD, has "good flow", while F5, containing the RIV-Me-β-CD inclusion complex, has only "acceptable flow". The other complex powders have a "satisfactory" flow, but in general all mixtures can be processed into tablets by direct compression [26].

The pharmacotechnical characteristics of the RIV-NIA-based samples are presented in Table 3.

Table 3.-Pharmacotechnical parameters of the RIV-NIA-based samples

Formulation	***Parameter***							
	Moisture content (%)	***Flowing time (sec)***	***Angle of repose (θ grade)***	***Flowing rate (g/s)***	***Bulk density (g/ml)***	***Tapped density (g/ml)***	***Carr index (CI) (%)***	***Hausner ratio (HR)***
RIV-NIA (1:1 cocrystallization compound)	5,22 ± 0,86	31,04 ± 0,17	44,15 ± 2,01	1,932	0,308	0,481	36,96	1,56
RIV-NIA (1:1 physical mixture)	2,81 ± 0,67	26,43 ± 0,25	35,24 ± 1,86	2,270	0,287	0,416	31,01	1,44
RIV-NIA (1:2 cocrystallization compound)	5,66 ± 0,73	30,12 ± 0,46	42,73 ± 2,33	1,992	0,340	0,502	32,27	1,47
RIV-NIA (1:2 physical mixture)	3,03 ± 0,34	25,08 ± 0,19	32,16 ± 1,41	2,392	0,315	0,477	33,96	1,51
F7	2,14 ± 0,33	18,36 ± 0,14	28,54 ± 1,04	3,267	0,521	0,673	22,58	1,29
F8	1,90 ± 0,15	17,27 ± 0,33	27,16 ± 1,58	3,474	0,494	0,655	24,58	1,32
F9	2,48 ± 0,65	16,85 ± 0,29	27,11 ± 1,22	3,560	0,530	0,692	23,41	1,30
F10	1,95 ± 0,70	14,12 ± 0,12	25,14 ± 2,38	4,249	0,517	0,668	22,60	1,29

*Stirring: 25 rpm, Nozzle: 15 mm

The relative moisture content drops to half of the values recorded for binary systems, which proves the influence of directly compressible excipients on this parameter and subsequently on the other physical properties influenced by it.

The flow improved considerably after mixing the binary systems with the selected excipients, which led to an increase in the speed. However, the materials containing the co-crystallizing compounds showed slightly lower flow performance compared to the materials based on physical mixtures.

All four binary systems showed poor flow (HR > 1.44) and high compressibility (CI > 31), with detectable differences between them. It is interesting to note that the materials containing the active ingredients with the lowest flow qualities (F7 and F10) showed the best improvement, and their recorded bulk and tap densities eventually became the highest of all samples [27].

7. Evaluation of the tablets obtained

7.1. Quality control of tablets

The pharmacotechnical characteristics of the six batches of RIV-CD compound tablets are presented in Table 4.

Table 4. - Qualitative characteristics of RIV-CD compound tablets

Parameter	***Formulation***					
	F1	***F2***	***F3***	***F4***	***F5***	***F6***
Thickness (mm)	2,71 ± 0,09	2,67 ± 0,11	2,70 ± 0,23	2,71 ± 0,34	2,69 ± 0,14	2,69 ± 0,36
Diameter (mm)	10 ± 0,25	10 ± 0,82	10 ± 0,19	10 ± 0,44	10 ± 0,30	10 ± 0,41
Mass uniformity (mg)	200 ± 1,68	199 ± 2,07	201 ± 1,05	200 ± 2,73	199 ± 1,54	200 ± 2,30
Hardness (N)	70 ± 2,85	86 ± 3,18	84 ± 3,67	67 ± 2,04	78 ± 3,09	85 ± 3,77
Friability (%)	0,05 ± 0,01	0,07 ± 0,03	0,07 ± 0,04	0,04 ± 0,02	0,10 ± 0,04	0,11 ± 0,03
***In vitro* disintegration time (seconds)**	35	40	88	97	123	145

In all six formulations, the tablets have a weight of approximately 200 mg, a diameter of 10 mm and a height of approximately 2.70 mm. The hardness varies between 67 N and 86 N and there is also a strong variation between batches of the same RIV-CD system. The friability of the tablets is more uniform between batches, but all values fall within the compendial limit (<1.0%). It is clear that all formulations containing the inclusion complexes require a shorter disintegration time than tablets containing the corresponding physical mixture.

The properties of the RIV-NIA tablets from the four batches are presented in Table 5.

Table 5.- Qualitative properties of the RIV-NIA tablets

Parameter	*Formulation*			
	F7	***F8***	***F9***	***F10***
Thickness (mm)	2,55 ± 0,06	2,52 ± 0,07	2,56 ± 0,03	2,59 ± 0,18
Diameter (mm)	10 ± 0,14	10 ± 0,21	10 ± 0,11	10 ± 0,19
Mass uniformity (mg)	200 ± 1,45	200 ± 2,32	200 ± 1,78	201 ± 2,94
Hardness (N)	8 ± 2,36	89 ± 2,88	1 ± 2,56	90 ± 2,15
Friability (%)	0,02 ± 0,01	0,05 ± 0,03	0,03 ± 0,02	0,06 ± 0,01
***In vitro* disintegration time (seconds)**	40	36	58	41

The tablets of each of the four formulations weigh approximately 200 mg, have a diameter of 10 mm and a height of 2.52-2.59 mm. The hardness varies from 71 N to 90 N, and the batches with the same molar ratio of RIV and NIA differ significantly from each other. The friability of the tablets does not vary significantly and all values are within the European Pharmacopoeia limit. Surprisingly, the disintegration time of the investigated formulations depends largely on the molar ratio of RIV to NIA and not on the hardness. However, the differences are not that great and, overall, all four batches showed excellent disintegration, with complete disintegration in less than one minute.

7.2.*In vitro* release profile

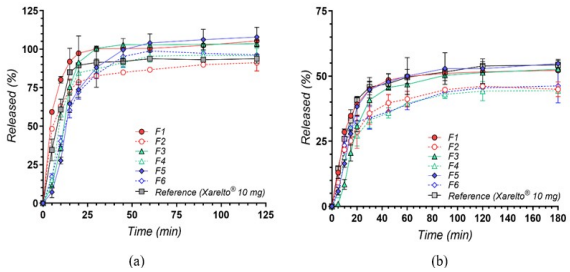

Figure 1. In vitro dissolution profiles of rivaroxaban from the tested formulations (F1–F6) compared to the reference product (Xarelto® 10 mg) in (a) sodium acetate buffer pH 4.5 with 0.2% SDS and (b) phosphate buffer pH 6.8.

Among the cyclodextrin-based products, the complexes (F1, F3, F5) consistently achieved higher or faster release compared to their corresponding physical mixtures (F2, F4, F6), demonstrating the advantage of preformed inclusion complexes in promoting drug wettability

and reducing crystallinity. By examining both dissolution configurations, it becomes evident that cyclodextrin-based formulations offer a distinct advantage in solubilizing rivaroxaban, especially when exogenous surfactants are absent.

(a) (b)

Figure 2-. Dissolution profiles of rivaroxaban from cocrystalline formulations (F7 and F9) and physical mixtures (F8 and F10) with nicotinamide, compared to pure rivaroxaban, in two different media: (a) pH 4.5 with 0.2% Tween 80 and (b) phosphate buffer pH 6.8. Each point represents the mean ± standard deviation (n = 3).

Overall, the successful preparation of rivaroxaban-nicotinamide cocrystals led to significantly improved dissolution profiles in acidic environments, supporting their potential to enhance the oral bioavailability of rivaroxaban.

CONCLUSIONS AND PERSONAL CONTRIBUTIONS

In this doctoral thesis, we aimed to increase the solubility of rivaroxaban in oral tablets by including it in different binary systems, inclusion complexes in three cyclodextrins (beta-cyclodextrin, hydroxypropyl-beta-cyclodextrin and methyl-beta-cyclodextrin) and co-crystallization compounds with niacinamide. The binary systems were characterized from a physicochemical and pharmacotechnical point of view, then they were incorporated as active ingredients in conventional tablets using direct compression technology. The development of solid pharmaceutical forms was achieved through extensive preformulation and formulation studies, and finally they were subjected to qualitative and quantitative control.

To establish dissolution performance, two test media were used: sodium acetate buffer pH 4.5, containing 0.2% sodium dodecyl sulfate (SDS) - the compendial condition for RIV 10 mg tablets, which means that sink conditions are met according to the compendial recommendations

for the analysis - and phosphate buffer pH 6.8, without surfactants, designed to mimic near-neutral intestinal environments. This second medium is not under sink conditions, but has high biorelevance for the behavior and performance of the drug in the gastrointestinal tract.

Among cyclodextrin-based products, the complexes (F1, F3, F5) consistently achieved higher or faster release compared to their corresponding physical mixtures (F2, F4, F6), demonstrating the advantage of preformed inclusion complexes in promoting drug wettability and reducing crystallinity.

At near-neutral buffer pH 6.8, without surfactant, more pronounced differences in formulation performance are highlighted, correlating with fasting conditions in the small intestine. Here, the influence of cyclodextrin complexation on drug release becomes more pronounced: the three complexes (F1, F3, F5) maintained noticeably higher dissolution rates and extents than their physical mixture counterparts (F2, F4, F6).

The dissolution profiles of rivaroxaban from co-crystalline formulations and physical mixtures with nicotinamide were evaluated compared to pure rivaroxaban in two different dissolution media (pH 4.5 and pH 6.8). Marked differences in dissolution performance were evident, influenced by both the formulation approach and the pH conditions of the media.

At pH 4.5, both co-crystallization formulations – F7 (1:1 molar ratio) and F9 (1:2 molar ratio) – demonstrated significantly improved dissolution compared to the corresponding physical mixtures (F8 and F10) and pure rivaroxaban.

In contrast, at pH 6.8, a notable reversal of dissolution performance was observed. In this near-neutral environment, the physical mixtures (F8 and F10) unexpectedly exhibited higher dissolution rates than the corresponding co-crystals (F7 and F9).

Overall, the successful preparation of rivaroxaban-nicotinamide co-crystals led to significantly improved dissolution profiles in acidic environments, supporting their potential to enhance the oral bioavailability of rivaroxaban.

The successful development of solid forms that exhibit improved dissolution under these physiologically relevant conditions supports their further investigation as promising oral dosage forms for thromboembolic therapy.

These findings support the continued exploration of cyclodextrin-based approaches to enhance the bioavailability of rivaroxaban tablets and may guide further optimization of

formulation parameters aimed at achieving both rapid and reliable drug release under physiologically relevant conditions.

The CD-containing formulations exhibited release profiles comparable to Xarelto® 10 mg, achieving similar dissolution performance without the need for SLS in the tablet formulation, thus offering a potentially improved safety profile.

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