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Review Article

BIOAVAILABILITY ENHANCEMENT STRATEGIES FOR RIVAROXABAN: A NOTEWORTHY REVIEW

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ABSTRACT

This review article discusses Rivaroxaban (RXB), an anticoagulant that has gained much attention due to its ability to prevent blood clots from forming in the body. However, one of the major challenges pharmaceutical companies face is the low water solubility of RXB, which can lead to difficulties in formulating the drug for oral administration and affect the drug's bioavailability. However, to the best of our knowledge, limited studies have explored enhancing the bioavailability of the RXB. Most of these studies have been purely academic and impractical for industrial use. Therefore, this review article aims to discuss successful studies that have increased the bioavailability of RXB. The goal is to inspire researchers to develop this new drug further. The article covers seven strategies for enhancing the bioavailability of RXB, including microspheres, liposomes, self-nano emulsifying drug delivery system, solid lipid nanoparticles, cocrystals, sustained release, and solid dispersion. The studies discussed in this review offer valuable insights into developing novel drug delivery systems that can help overcome the limitations of existing drugs.

Keywords: Rivaroxaban, Bioavailability enhancement, Microspheres, Liposomes, Self-nanoemulsifying drug delivery system, Solid lipid nanoparticles, Cocrystals, Sustained release, Solid dispersion

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INTRODUCTION

Rivaroxaban (RXB) (fig. 1) is a drug that has gained a lot of attention in recent years due to its ability to prevent blood clots from forming in the body. It is a type of anticoagulant that works by inhibiting the activity of a protein called factor Xa. This protein is responsible for the formation of blood clots, so by inhibiting its activity, RXB helps to prevent clots from forming [1]. The discovery of RXB was a long and complicated process that involved many scientists and researchers. The drug was first synthesized in the 2000s by a team of chemists at Bayer AG, a Germany pharmaceutical company. These chemists were looking for a new type of anticoagulant that could be taken orally and would not require frequent monitoring [2]. After several years of testing and refining, RXB was found to be effective at preventing blood clots in patients with atrial fibrillation, a condition that causes an irregular heartbeat. The drug was also found to be effective at preventing deep vein thrombosis (DVT) and pulmonary embolism, two conditions that can be life-threatening if left untreated [3, 4].

In 2011, the FDA approved RXB for use in patients with atrial fibrillation and in those who had undergone hip or knee replacement surgery. Since then, the drug has been approved for use in a variety of other medical settings, including the treatment of deep vein thrombosis and pulmonary embolism. Recently, RXB has been used to prevent disease progression in hospitalized patients with Coronavirus disease (Covid-19), as well as to prevent thrombosis in non-valvular atrial fibrillation (NVAF) patients and obese patients [5, 6].

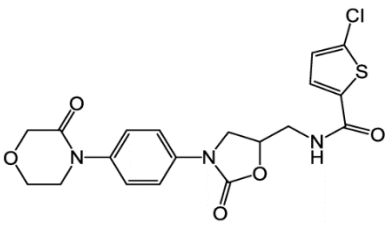

Fig. 1: Rivaroxaban structure

However, one of the major challenges faced by pharmaceutical companies is the poor water solubility of RXB. This can lead to difficulties in formulating the drug for oral administration and can also affect the drug's bioavailability. As a pharmaceutics expert, we understand the importance of solubility in drug development. When a drug is not soluble in water, it can be difficult to formulate it in a way that is both effective and safe for patients. This is particularly true for RXB, which has a low water solubility. RXB has been classified under the biopharmaceutical classification system as a class II drug [3]. From a pharmaceutical sciences point of view, this classification system is crucial in determining the drug's absorption and bioavailability. Class II drugs like RXB have low solubility but high permeability, meaning they are struggle dissolved in water but easily to pass through intestinal cell membranes. This can lead to variable absorption rates and reduced bioavailability for the drug. Moreover, the biopharmaceutical classification system also plays a significant role in the development of generic versions of RXB. As the classification system provides valuable information on the drug's properties, it enables scientists to develop more efficient generic formulations that can be used as an alternative to the brand-name drug. One of the key factors that determine the effectiveness of RXB is its bioavailability. Bioavailability refers to the amount of a drug that is absorbed into the bloodstream and is available to exert its therapeutic effect. For RXB, bioavailability is affected by several factors, including the route of administration, food intake, and drug interactions [5, 7].

The bioavailability of RXB is only 60% of the drug is absorbed under fasting conditions when taken in a 20 mg dose. However, the bioavailability of RXB is dose-dependent and food-dependent, with 90% absorption for a 10 mg dose and 100% absorption for a 5 mg dose. In terms of drug interactions, RXB can interact with other medications that affect the activity of factor Xa. For example, other anticoagulant medications, such as warfarin or heparin, can increase the risk of bleeding when taken with RXB. Other medications that affect the liver, such as rifampin or carbamazepine, can decrease the bioavailability of RXB [7, 8].

However, to the best of our knowledge, there are limited studies that have explored enhancing the bioavailability of the RXB (fig. 2). Most

of these studies have been purely academic and not practical for industrial use. Therefore, this review article aims to discuss successful studies that have increased the bioavailability of RXB. The goal is to inspire researchers to further develop this new drug.

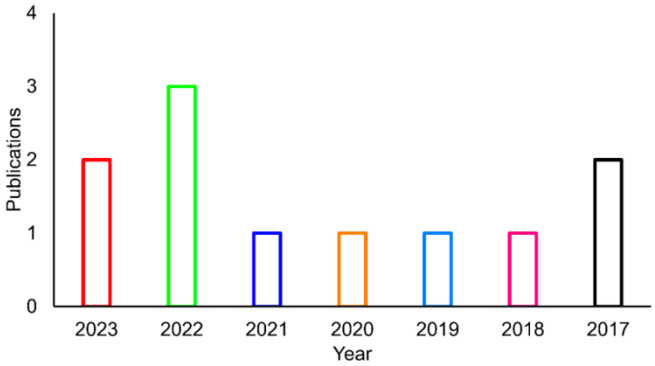

Fig. 2: Cumulative number of publications on enhanced oral bioavailability of rivaroxaban. The number of publications was determined by searching the PubMed database (https://pubmed.ncbi.nlm.nih.gov) on 12 July 2023

Microspheres

The use of microspheres technology has proven to be a promising approach for enhancing the bioavailability of drugs. Microspheres are tiny, spherical particles that can be loaded with drugs and delivered to the targeted site in the body [9]. Fig. 3 show the format for liposome imaging. In recent years, microspheres have been extensively studied for their potential in improving the delivery of various types of drugs, including poorly soluble drugs, peptides, and proteins. The use of microspheres has also shown promising results in reducing the toxicity and side effects of drugs by targeting specific sites in the body [10].

In a recent study by Choi *et al.*, focused on the development of microspheres to enhance the solubility, dissolution, and oral bioavailability of RXB. The microspheres were created using water-soluble carriers and surfactants. The researchers found that the molecular interactions between RXB, poly-vinylpyrrolidone K30, (PVP), and surfactant sodium lauryl sulfate (SLS) were crucial in improving RXB solubility, dissolution, and oral bioavailability. The optimized RXB/PVP/SLS ratios in formulations resulted in significant improvements in solubility and dissolution rates compared to RXB powder. Moreover, the oral bioavailability of RXB was improved by 2.4-and 1.7-fold compared to that of RXB powder. These findings imply that optimizing the drug-to-excipient ratio can lead to successful formula development. Overall, the microspheres developed in this study successfully enhanced the solubility, dissolution rate, and bioavailability of RXB [11].

Liposomes

Recent advancements in drug delivery have led to the discovery of liposomes as a promising method for improving drug bioavailability. Liposomes are small, spherical vesicles that can encapsulate drugs and transport them to specific sites within the body. This technology is particularly useful for drugs that have poor solubility or are quickly metabolized by the body. By incorporating drugs into liposomes, we can improve their stability, prolong their circulation time, and enhance their therapeutic efficacy [12].

The study conducted by Elsayad *et al.*, the researchers developed chitosan-caged liposomes to enhance the oral bioavailability of RXB in the fasted condition. The selected formulation (RXB-SF), composed of Phospholipid S100/Tween 80 and coated with Chitosan solution. *In vitro* release studies of RXB from the RXB-SF were also conducted and found to retard RXB release while also improving stability and sustained release characteristics. Compared to RXB suspension, RXB-SF showed no statistically significant difference in pharmacokinetic parameters in fast and fed test animals. The bioavailability of RXB with RXB-SF improved by 59.66% and 26.97% in the fed and fast states, respectively, compared to RXB suspension in the fed state. The results suggest the efficacy of the prepared liquid formula in improving the oral bioavailability of RXB regardless of the fed state and its potential use as a pediatric formulation of RXB [13].

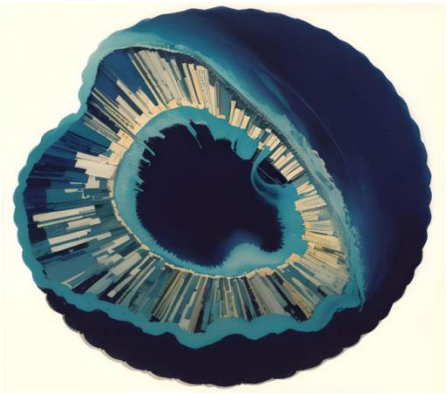

Fig. 3: Format of liposome imaging

Self-nanoemulsifying drug delivery system

Self-Nanoemulsifying Drug Delivery System (SNEDDS) is a promising approach for enhancing drug bioavailability. SNEDDS are composed of oil, surfactant, and co-surfactant, which can self-emulsify in the gastrointestinal tract, forming fine droplets that enhance drug solubility and absorption. This technology has been shown to improve the oral bioavailability of poorly soluble drugs, reducing the required dose and minimizing side effects. SNEDDS has also shown to be effective in enhancing the bioavailability of drugs that are sensitive to enzymatic degradation. With its potential to improve drug efficacy and patient compliance, SNEDDS is a promising tool for developing novel drug delivery systems [14-16].

The study conducted by Xue *et al.* focused on the development of a self-nanoemulsifying drug delivery system (SNEDDS) to enhance the oral bioavailability of RXB and reduce the food effect. The researchers selected oil, surfactant, and co-surfactant based on a saturated solubility study, with Tween80, and 1,2-propanediol being chosen as the final components. The pseudo-ternary-phase diagram was utilized to optimize the preliminary composition of the SNEDDS formulation, and the optimized RXB-SNEDDS formulation was selected using central composite design (CCD) of response surface methodology. The drug dissolution profile was compared to the commercial formulation Xarelto® in four different media (pH 1.2HCl, pH 4.5NaAc-HAc, pH 6.8PBS, and water). The results showed that the SNEDDS formulation had successfully increased the drug solubility in all four media. *In vivo* pharmacokinetics studies of

SNEDDS formulation and Xarelto® were carried out in adult beagle dogs, and it was observed that RXB with no food effect was achieved in SNEDDS formulation compared with Xarelto® in fed state. Hence, the researchers concluded that the SNEDDS formulation developed in this study is useful in enhancing the oral bioavailability and reducing the food effect in a fasted state [17].

Solid lipid nanoparticles (SLNs)

The use of Solid Lipid Nanoparticles (SLNs) has proven to be a promising approach in enhancing drug bioavailability. SLNs are composed of biodegradable lipids and are characterized by their small size, high surface area, and ability to encapsulate both hydrophilic and hydrophobic drugs. Due to their unique properties, SLNs have been shown to improve drug solubility, stability, and absorption, leading to enhanced therapeutic efficacy [18].

In a study by Luo *et al.*, to improve RXB biopharmaceutical profile, the researchers developed RXB-loaded SLNs (RXB-SLNs) using a high-pressure homogenizer. The RXB-SLNs were then investigated to an *in vitro*, ex-vivo, and *in vivo* evaluations, prothrombin time assessment, and toxicity. The results showed that the *in vitro* release profiles of the RXB-SLNs exhibited enhanced dissolution (89±9.91%) as compared to pure drug (11±1.43%) after 24 h of the study. The PK study demonstrated a 7 times enhanced bioavailability of RXB-SLNs when compared with a pure drug. Furthermore, RXB-SLNs exhibited an expressive anti-coagulant behavior in human and rat blood plasma. Also, the final formulation exhibited no toxicity after oral administration of the SLNs. Overall, these findings suggest that RXB-SLNs have the potential to carry the RXB with enhanced therapeutic efficacy and no toxicity, specifically for the treatment of deep vein thrombosis. This study provides valuable insight into the development of novel drug delivery systems that can help overcome the limitations of existing drugs [19].

Cocrystals

Cocrystals have been introduced as an approach to improving drug delivery. These solid-state materials are composed of two or more crystallized components in a specific stoichiometric ratio. By combining drug molecules with comforters, cocrystals can modulate the physicochemical properties of drugs, such as solubility and stability, leading to enhanced bioavailability. Moreover, cocrystals can provide unique advantages over traditional drug delivery systems, such as improved drug targeting and reduced toxicity. With their ability to enhance drug performance, cocrystals offer tremendous potential for advancing drug delivery and efficacy in various therapeutic areas [20].

In the study by Meng *et al.*, five cocrystals of RXB were prepared using three organic acids p-hydroxybenzoic acid (HBA), 2,4-dihydroxybenzoic acid (DBA), and succinic acid (SA) with two organic bases nicotinamide (NA), and isonicotinamide (IA) as coformers. The cocrystals were prepared by liquid-assisted grinding, and their physical mixture (PMs) was prepared by gently mixing in a plastic bag. The study provides valuable insights into the dissolution pattern of cocrystals under sink and non-sink conditions. Interestingly, RXB-HBA, RXB-DBA and RXB-SA cocrystals showed an obvious "spring and parachute" pattern with a faster initial dissolution state and a prolonged drug supersaturation state. The study also found that the Intrinsic dissolution of RXB cocrystals indicated a solubility improvement effect of cocrystals with promising chemical and physical properties rather than simple physical mixtures. In addition, the impact of cocrystals on drug membrane permeability was investigated using epithelial cellular models. The study found that cocrystals can either improve, decrease, or have no significant impact on the membrane permeability of drugs, and the mechanisms behind this phenomenon are yet to be fully understood. Interestingly, the solubility of cocrystals was not always positively related to permeability. The study also compared the behavior of cocrystals with physical mixtures and found that the latter formed molecular aggregates in solution, leading to different results. Based on the results of solubility, dissolution, and monolayer cell membrane permeability studies, RXB-HBA, and RXB-DBA cocrystals were selected for further pharmacokinetic studies in beagle dogs. The study found that the bioavailability of RXB-DBA cocrystal and RXB-HBA cocrystals was higher than raw RXB, thus indicating a promising perspective for further formulation development. However, the study demonstrated the successful preparation of RXB cocrystals and their improved dissolution behavior, which could potentially improve their *in vivo* absorption behavior [6].

Sustained release

Sustained release drug delivery systems have the potential to improve patient outcomes by providing a more controlled and targeted release of drugs over an extended period of time. By utilizing sustained-release technology, drug doses can be optimized and side effects minimized, leading to better treatment outcomes and improved patient compliance [21].

Anwar *et al.* conducted a study on the optimization of RXB-loaded PLGA NPs using central composite design (CDD) based on five responses: particle size, PDI, ZP, EE, and drug loading. They developed thirteen formulas using Expert Design® software, with varying particle size, PDI, ZP, %EE, and %DL. Formula F8 was found to be optimal, with a particle size of 496 nm, PDI of 0.607, ZP of 18.41 mV, EE of 87.91%, and DL of 9.5%. This formula contained PLGA (125 mg), PVA (0.5% w/v), and 20 mg of RXB. *In vitro* release studies showed enhanced sustained release of RXB from RXB-PLGA-NPs (F8) compared to a marketed tablet XARELTO® (68.45% vs. 97.64% after 48 h, respectively). Pharmacokinetic studies in rats showed that RXB-loaded PLGA NPs successfully enhanced the bioavailability of RXB with no food effect. The developed nanoparticles have the potential for better therapeutic efficiency with no food effect [22].

Solid dispersion

Solid dispersion is a promising approach to improving drug bioavailability, particularly for drugs with poor solubility. Solid dispersion technology offers several advantages over traditional drug delivery systems, such as tablets or capsules. For example, it can improve drug release kinetics, allowing for a more controlled and sustained release of medication. However, the use of solid dispersion technology in drug delivery represents an exciting area of research and development. By improving drug bioavailability, solid dispersion has the potential to enhance patient treatment outcomes and improve overall health outcomes [23].

In study conducted by Shah *et al.*, the potential of solid dispersion adsorbate (SDA) to improve the solubility and bioavailability of RXB was evaluated. The study utilized a 32 full factorial design to formulate various SDAs, with the amount of carrier and amount of adsorbent as the selected independent variables and the time required for 85% drug release and saturated solubility as the measured responses. Cytotoxicity studies were conducted on Caco-2 cells using MTT assay, while *in vivo* pharmacokinetics and pharmacodynamic evaluations were carried out to assess the prepared SDA. The results showed that the prepared RXB SDA tablets had improved oral bioavailability and could be an alternate approach of solid dosage form for its development for commercial application. The study also confirmed the nontoxicity of prepared RXB SDA tablets. Overall, the findings suggest that RXB SDA tablets have the potential to enhance the bioavailability of RXB, and this study provides a valuable contribution to the field of solid dosage form development [24].

Comparison of studies on drug delivery systems

In this comparison, we will analyze seven different drug delivery systems and their potential for enhancing RXB bioavailability. Table 1 summarize the findings of each study and compare them based on their effectiveness in improving drug solubility, dissolution rate, and bioavailability.

Overall, each drug delivery system has its unique advantages and disadvantages. Microspheres and liposomes offer promising results in enhancing drug bioavailability. Self-nanoemulsifying drug delivery system and solid lipid nanoparticles show improvements in drug solubility and bioavailability. Cocrystals offer a unique approach to improving drug delivery, while sustained release and

solid dispersion improve drug release kinetics. In summary, each system has the potential to enhance drug efficacy and patient compliance, and further research is needed to determine the most effective drug delivery system for a specific drug.

Table 1: Compares studies on enhancing the bioavailability of rivaroxaban

Drug delivery system	Study	Key findings
Microspheres	Choi *et al.* [11]	Improved solubility, dissolution rate, and bioavailability of RXB by optimizing drug-to-excipient ratio.
Liposomes	Elsayad *et al.* [13]	Chitosan-caged liposomes improved oral bioavailability of RXB by 59.66% and 26.97% in the fed and fast states, respectively, compared to RXB suspension in the fed state.
Self-Nanoemulsifying Drug Delivery System (SNEDDS)	Xue *et al.* [17]	SNEDDS formulation increased RXB solubility in all four media and improved oral bioavailability of RXB with no food effect in fasted state.
Solid Lipid Nanoparticles (SLNs)	Luo *et al.* [19]	RXB-SLNs enhanced dissolution (89±9.91%) as compared to pure drug (11±1.43%) after 24 h of the study, and the PK study demonstrated a 7 times enhanced bioavailability of RXB-SLNs when compared with a pure drug.
Cocrystals	Meng *et al.* [6]	RXB-HBA and RXB-DBA cocrystals were selected for further pharmacokinetic studies in beagle dogs, and the bioavailability of RXB-DBA cocrystal and RXB-HBA cocrystals was higher than raw RXB.
Sustained Release	Anwar *et al.* [22]	RXB loaded PLGA NPs successfully enhanced the bioavailability of RXB with no food effect.
Solid Dispersion	Shah *et al.* [24]	RXB SDA tablets improved oral bioavailability and could be an alternate approach of solid dosage form for its development for commercial application.

CONCLUSION

In conclusion, the enhancement of Rivaroxaban (RXB) bioavailability is a crucial aspect of drug development. Several strategies have been developed to achieve this, including the use of microspheres, liposomes, self-nanoemulsifying drug delivery systems (SNEDDS), solid lipid nanoparticles (SLNs), cocrystals, sustained release, and solid dispersion. These strategies have been shown to improve RXB solubility, dissolution rate, and oral bioavailability in various studies. The optimized drug-to-excipient ratio is crucial in the successful development of these formulations. The findings of these studies suggest that these novel drug delivery systems have the potential to overcome the limitations of existing drugs and improve therapeutic efficacy with no toxicity. Further research and development in this field can lead to the commercial application of these formulations, leading to better treatment options for patients.

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Nil

AUTHORS CONTRIBUTIONS

The members of the research team have confirmed that they made equal contributions to the study.

CONFLICT OF INTERESTS

We, the authors of this manuscript, declare that there is no conflict of interest between us. We have no financial or personal relationships that could inappropriately influence our work. We have given full disclosure of any potential conflicts of interest to the Journal of International Journal of Applied Pharmaceutics. We are committed to ensuring the integrity and objectivity of our research and writing, and we stand behind the accuracy and validity of our findings.

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