RESEARCH PAPER

# Development and Evaluation of a pH-Responsive Nano suspension of Rivaroxaban for Enhanced Oral Delivery

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***Abstract***
Rivaroxaban, a Biopharmaceutics Classification System (BCS) Class II drug, exhibits poor aqueous solubility, leading to variable oral bioavailability and suboptimal therapeutic performance. The present study aimed to develop and evaluate a pH-responsive nanosuspension of rivaroxaban to enhance its solubility, dissolution rate, and intestinal drug release. Nanosuspension was prepared using the antisolvent precipitation method combined with high-speed homogenization and ultrasonication. Preformulation studies confirmed poor aqueous solubility and crystalline nature of the drug. Compatibility studies using FTIR and DSC indicated no significant interaction between drug and excipients. The optimized formulation exhibited a particle size of 182 nm with a low polydispersity index (0.24), indicating uniform distribution. Zeta potential was found to be −32.6 mV, suggesting good physical stability. The formulation showed high drug content (98.3%) and entrapment efficiency (88.3%). In-vitro dissolution studies demonstrated minimal drug release in acidic conditions and significantly enhanced release (~96%) in intestinal pH, confirming pH-responsive behavior. Stability studies indicated negligible changes in physicochemical parameters over time. The results suggest that the developed nanosuspension is a promising strategy for improving the oral delivery of rivaroxaban and other poorly soluble drugs.

**Keywords:** Nanosuspension, pH responsive polymer, rivaroxaban

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## INTRODUCTION

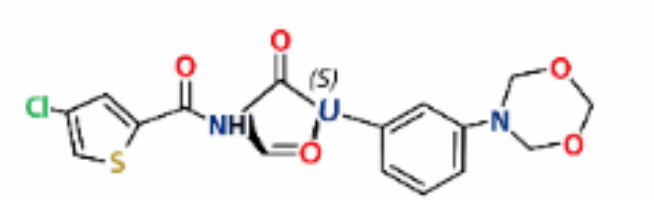


**Fig. 1 Molecular Structure of Rivaroxaban**

Oral drug delivery continues to be the most preferred route of administration due to its convenience, patient compliance, and cost-effectiveness. However, the therapeutic success of many orally administered drugs is often limited by poor aqueous solubility and variable gastrointestinal absorption [1]. This challenge is particularly evident in Biopharmaceutics Classification System (BCS) Class II drugs, where dissolution becomes the rate-limiting step for absorption. Among such drugs, rivaroxaban—a widely prescribed oral anticoagulant—exhibits low solubility in aqueous media, leading to inconsistent bioavailability and interindividual variability in therapeutic response [2]. These limitations highlight the need for innovative formulation strategies that can enhance solubility while enabling controlled and site-specific drug release.

In recent years, nanosuspension technology has emerged as a promising approach to address solubility-related challenges. By reducing drug particles to the nanometer scale, nanosuspensions significantly increase surface area, thereby improving dissolution rate and saturation solubility [3]. Additionally, the use of suitable stabilizers enhances particle wettability and prevents aggregation, contributing to improved physicochemical stability [4]. Despite these advantages, conventional nanosuspensions may still

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face challenges related to premature drug release in the acidic gastric environment, which can limit their efficiency for drugs that are better absorbed in the intestine.

To overcome this limitation, the integration of pH-responsive polymers into nanosuspension systems offers a more advanced and physiologically aligned strategy. These polymers are designed to remain intact in acidic gastric conditions while facilitating drug release in the more neutral to slightly alkaline environment of the intestine [5]. Such a targeted release mechanism not only protects the drug from unfavorable gastric conditions but also promotes site-specific delivery, thereby enhancing absorption and therapeutic efficacy. This dual approach—combining nanosizing with pH-responsive behavior—represents a rational and innovative solution for improving the oral performance of poorly soluble drugs like rivaroxaban [6,7].

The present study is therefore aimed at developing, optimizing, and evaluating a pH-responsive nanosuspension of rivaroxaban to enhance its solubility, dissolution rate, and overall oral delivery performance. A systematic approach has been adopted, beginning with preformulation studies to understand the physicochemical characteristics of the drug, followed by the development of a robust analytical method for its estimation. The formulation strategy focuses on selecting appropriate stabilizers and enteric polymers, optimizing process variables, and producing nanosized particles with desirable stability and performance characteristics.

Comprehensive evaluation of the developed nanosuspension includes particle size analysis, zeta potential measurement, morphological assessment, and determination of drug content and entrapment efficiency. Furthermore, in-vitro dissolution studies in simulated gastric and intestinal conditions are designed to assess the pH-responsive release behavior and compare it with the pure drug. Stability studies conducted as per regulatory guidelines aim to ensure the robustness and shelf-life of the formulation.

Through this integrated approach, the study seeks to demonstrate that a pH-responsive nanosuspension system can significantly improve the solubility and dissolution behavior of rivaroxaban while enabling controlled intestinal release. Ultimately, this research contributes to the growing field of nanotechnology-based drug delivery systems and offers a potential pathway for enhancing the therapeutic performance of oral anticoagulants.

## MATERIALS AND METHODS

This study was designed to systematically develop and evaluate a pH-responsive nanosuspension of rivaroxaban with the objective of improving its solubility, dissolution behavior, and intestinal drug release. The experimental methodology was carefully structured based on established nanosuspension principles and pharmacopeial guidelines to ensure reproducibility, accuracy, and scientific rigor.

### Materials

Rivaroxaban (API grade, purity ≥ 99%) was kindly provided as a gift sample by Tablets India, Chennai. pH-responsive polymers, including Eudragit L100, Eudragit S100, and Hydroxypropyl Methylcellulose (HPMC K15M), were selected due to their well-known enteric properties, enabling minimal drug release in acidic environments and enhanced release at intestinal pH.

Stabilizers and surfactants such as Poloxamer 188, Tween 80, Polyvinyl Alcohol (PVA), and Sodium Lauryl Sulfate (SLS) were employed to improve wettability and stabilize the nanosuspension. Analytical grade solvents and reagents, including ethanol, methanol (HPLC grade), distilled water, hydrochloric acid (0.1 N), sodium hydroxide (0.1 N), and phosphate buffer salts, were used throughout the study without further purification.

### Methods

#### Preformulation Studies

Preformulation studies were conducted to understand the fundamental physicochemical properties of rivaroxaban that could influence formulation development [8].

***Organoleptic properties*** such as color, appearance, odor, and texture were evaluated visually. The drug appeared as a white to slightly yellow crystalline powder.

***Melting point determination*** was performed using the capillary method, and the observed values were compared with reported literature to confirm drug identity and purity.

***Solubility studies*** were carried out by adding excess drug to various media, including distilled water, 0.1 N hydrochloric acid (pH 1.2), phosphate buffer (pH 6.8 and 7.4), methanol, and ethanol. Samples were equilibrated, filtered, and analyzed to determine the solubility profile.

***Drug–Excipient Compatibility Studies***

Compatibility between rivaroxaban and selected excipients was evaluated to ensure formulation stability [9].

**FTIR spectroscopy** was performed using the KBr pellet method over a spectral range of 4000–400 $cm^{-1}$. Spectra of pure drug, physical mixtures, and optimized formulation were compared to identify any potential chemical interactions.

**Differential Scanning Calorimetry (DSC)** analysis was carried out to study the thermal behavior of the drug and detect any polymorphic transitions or incompatibilities with excipients.

#### Preparation of pH-Responsive Nanosuspension

The nanosuspension was prepared using the antisolvent precipitation method combined with high-speed homogenization, selected for its suitability in handling poorly soluble drugs and its scalability [10, 11,12].

Initially, speified quantity of rivaroxaban was dissolved in ethanol to form the organic phase, followed by the addition of the selected pH-responsive polymer (e.g., Eudragit L100). The solution was stirred continuously to ensure complete dissolution.

Separately, an aqueous phase was prepared by dissolving the stabilizer (Tween 80) in distilled water under controlled temperature conditions (25 ± 2°C).
The organic phase was then injected dropwise into the aqueous phase under constant stirring, resulting in rapid supersaturation and nanoparticle formation. This was followed by high-speed homogenization (10,000–18,000 rpm) to further reduce particle size and improve uniformity.
Subsequently, probe sonication was performed in pulse mode (5 seconds ON / 5 seconds OFF) to minimize aggregation and enhance dispersion stability.
Residual solvent was removed by continuous stirring at room temperature or under reduced pressure. The nanosuspension was then freeze-dried using mannitol (3%) as a cryoprotectant. Samples were frozen at –40°C and lyophilized for 24 hours to improve stability and shelf-life.

**Optimization of Formulation**
Multiple batches were prepared by varying critical formulation parameters such as drug-to-polymer ratio, stabilizer concentration, homogenization speed, and sonication time. The optimized formulation was selected based on key performance indicators, including particle size, zeta potential, entrapment efficiency, and dissolution profile.

**Evaluation of Nanosuspension**
The developed nanosuspension was subjected to comprehensive characterization [13 -15].

**Particle size and polydispersity index (PDI)** were determined using dynamic light scattering at 25°C after appropriate dilution. A PDI value below 0.3 indicated uniform particle distribution.

**Zeta potential** was measured using electrophoretic mobility to assess surface charge and predict stability. Values greater than ±30 mV were considered indicative of good stability.

**Morphological analysis** was performed using scanning electron microscopy to observe particle shape and surface characteristics.

**Drug content** was determined by diluting the nanosuspension with methanol, followed by filtration and spectrophotometric analysis.

**Entrapment efficiency** was evaluated using the centrifugation method. Samples were centrifuged at 15,000 rpm for 30 minutes, and the supernatant was analyzed for free drug content. Entrapment efficiency was calculated based on the difference between total and free drug.

**In Vitro Dissolution and Release Studies**
Dissolution studies were conducted using USP Dissolution Apparatus II at 37 ± 0.5°C with a paddle speed of 50 rpm [16]. The study was performed in a sequential pH environment, beginning with simulated gastric fluid (pH 1.2) for 2 hours, followed by simulated intestinal fluid (pH 6.8).
Samples were withdrawn at predetermined intervals, filtered, and analyzed spectrophotometrically at 260 nm. The cumulative drug release was calculated and compared with that of the pure drug to assess enhancement in dissolution.
The pH-responsive behavior was evaluated by comparing drug release profiles in acidic and intestinal conditions, confirming minimal release in gastric pH and enhanced release in intestinal pH.

**Stability Studies**
Stability studies were conducted to assess the robustness of the optimized formulation. Samples were stored under refrigerated (4°C), room temperature, and accelerated conditions (40°C ± 2°C / 75% RH ± 5%) for three months [17].
At predetermined intervals, samples were analyzed for particle size, PDI, zeta potential, drug content, and physical appearance to evaluate any changes over time.

**Statistical Analysis**
All experiments were performed in triplicate, and the results were expressed as mean ± standard deviation. Statistical analysis was carried out using analysis of variance (ANOVA), with significance determined at appropriate confidence levels [18, 19].

## RESULTS AND DISCUSSION

**Preformulation Studies**
Preformulation studies of rivaroxaban was carried out to establish its baseline physicochemical properties and to guide formulation development. The drug was observed as a white to off-white, odorless crystalline powder with a fine texture, indicating its highly ordered crystalline nature. Such crystallinity is typically associated with poor aqueous solubility and low dissolution rate, thereby necessitating particle size reduction strategies.

**Table 1 Organoleptic properties of rivaroxaban**

| Parameter | Observation |
|---|---|
| Color | White to off-white |
| Odor | Odorless |
| Nature | Crystalline powder |
| Texture | Fine and smooth |

The melting point of rivaroxaban was found to be in the range of 228–230°C, which is in close agreement with reported literature values, confirming the purity and identity of the drug. The sharp melting endotherm further supports its crystalline structure.

**Table 2 Melting point of rivaroxaban**

| Sample | Observed Melting Point (°C) | Reported Value (°C) |
|---|---|---|
| Rivaroxaban | 230–233 | 228–234 |

Solubility analysis revealed that rivaroxaban exhibits poor aqueous solubility in distilled water and acidic medium (pH 1.2), while relatively higher solubility was observed in phosphate buffer (pH 6.8). The drug showed high solubility in organic solvents such as methanol and ethanol. This solubility behavior is characteristic of BCS Class II drugs, where dissolution is the rate-limiting step for absorption. These findings strongly justify the development of a formulation approach aimed at enhancing dissolution and enabling site-specific drug release.

**Table 3 Solubility studies of rivaroxaban**

| Medium | Solubility (mg/mL) | Interpretation |
|---|---|---|
| Distilled Water | Very low | Poor aqueous solubility |
| pH 1.2 | Low | Limited gastric solubility |
| pH 6.8 | Moderate | Improved intestinal solubility |
| Methanol | High | Freely soluble |
| Ethanol | High | Freely soluble |

**Drug–Excipient Compatibility Studies**

***FTIR Analysis***

FTIR spectra of pure rivaroxaban exhibited characteristic absorption bands corresponding to functional groups such as carbonyl (C=O), amide, aromatic C–H, and N–H stretching vibrations. These peaks were retained in the spectra of physical mixtures and optimized formulations without any significant shifts or disappearance (Table 4 & 5).

**Table 4 Major Characteristic Peaks**

| Wavenumber ($cm^{-1}$) | Functional Group | Assignment |
|---|---|---|
| 3330–3200 | N–H stretching | Secondary amide |
| 3060 | Aromatic C–H stretching | Aromatic ring |
| 1735 | C=O stretching | Oxazolidinone carbonyl |
| 1650 | Amide C=O stretching | Amide group |
| 1595 | C=C stretching | Aromatic ring |
| 1350–1380 | C–N stretching | Amine |
| 1250–1100 | C–O stretching | Ether linkage |

**Table 5 Major Observed Peaks in Physical Mixture**

| Wavenumber ($cm^{-1}$) | Assignment | Observation |
|---|---|---|
| 3325 | N–H stretching (Drug) | Present, slight broadening |
| 1730 | C=O stretching (Drug) | Present |
| 1705 | C=O stretching (Polymer) | Present |
| 1250–1150 | C–O stretching | Present |
| 2950 | C–H stretching | Present |

The preservation of these characteristic peaks confirms the chemical integrity of rivaroxaban during formulation. Minor peak broadening observed in the physical mixture suggests weak intermolecular interactions, such as hydrogen bonding, rather than any chemical incompatibility. The absence of new peaks or

significant spectral changes indicates that no chemical interaction occurred between the drug and excipients.

***DSC Analysis***

DSC thermograms of pure rivaroxaban exhibited a sharp endothermic peak corresponding to its melting point, confirming its crystalline nature. In contrast, the nanosuspension showed reduced peak intensity and slight broadening.

This reduction in crystallinity is indicative of partial amorphization induced during the nanosizing process. The amorphous form is generally associated with improved solubility and dissolution properties. Overall, DSC findings corroborate the FTIR results, confirming drug–excipient compatibility and formulation stability.

**Table 6 DSC of rivaroxaban and nanosuspension**

| Sample | Peak Temperature (°C) | Observation |
|---|---|---|
| Pure Drug | ~231 | Sharp peak |
| Nanosuspension | Reduced intensity | Slight broadening |

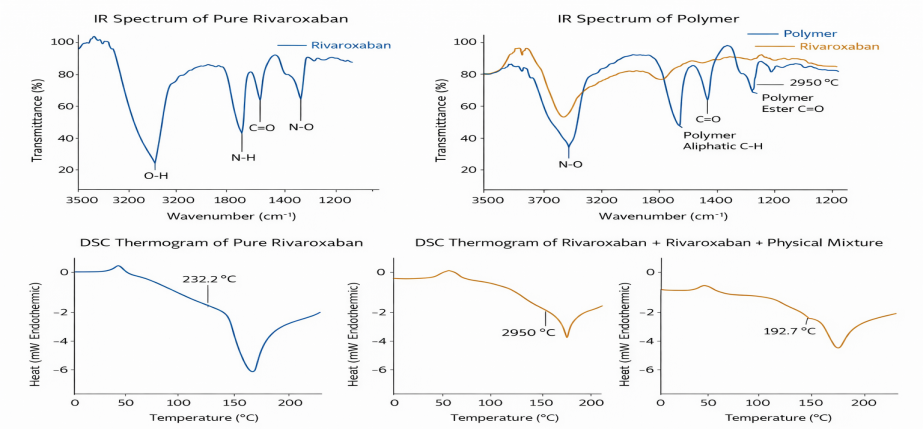


**Fig. 2 FTIR and DSC spectra of drug and physical mixture**

**Optimization of Formulation**

A series of formulation batches (F1–F6) were prepared by varying polymer concentration, stabilizer concentration, and homogenization speed (Table 7). The objective was to identify an optimized formulation with minimal particle size, narrow size distribution, and enhanced dissolution characteristics.

Among all batches, formulation F6 demonstrated superior performance across all evaluated parameters. The results highlight the critical influence of polymer and stabilizer concentration, as well as processing conditions, on nanosuspension characteristics. Optimal homogenization and sonication conditions were essential for achieving uniform nanoscale particles.

**Table 7 Composition of Trial Batches**

| Batch | Drug (mg) | Polymer (%) | Stabilizer (%) | Homogenization Speed (rpm) |
|---|---|---|---|---|
| F1 | 100 | 0.5 | 0.5 | 10,000 |
| F2 | 100 | 1.0 | 0.5 | 12,000 |
| F3 | 100 | 1.0 | 1.0 | 15,000 |
| F4 | 100 | 1.5 | 1.0 | 15,000 |
| F5 | 100 | 1.5 | 1.5 | 18,000 |
| F6 (Optimized) | 100 | 1.0 | 1.0 | 15,000 |

**Particle Size and Polydispersity Index**

Particle size analysis using dynamic light scattering revealed a significant reduction in particle size from the micrometer range to the nanometer scale. The optimized formulation exhibited an average particle size of 182 ± 5 nm with a polydispersity index (PDI) of 0.24 (Table 8).

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The low PDI value indicates a narrow and uniform particle size distribution, which is essential for ensuring reproducibility, consistent dissolution, and physical stability. The reduction in particle size significantly increases the surface area, thereby enhancing dissolution rate in accordance with the Noyes–Whitney equation

**Table 8 Particle Size Analysis**

| Batch | Particle Size (nm) | PDI |
|---|---|---|

| Batch | Particle Size (nm) | PDI |
|---|---|---|
| F1 | 480 | 0.52 |
| F2 | 320 | 0.41 |
| F3 | 210 | 0.28 |
| F4 | 240 | 0.32 |
| F5 | 190 | 0.35 |
| F6 | 182 | 0.24 |

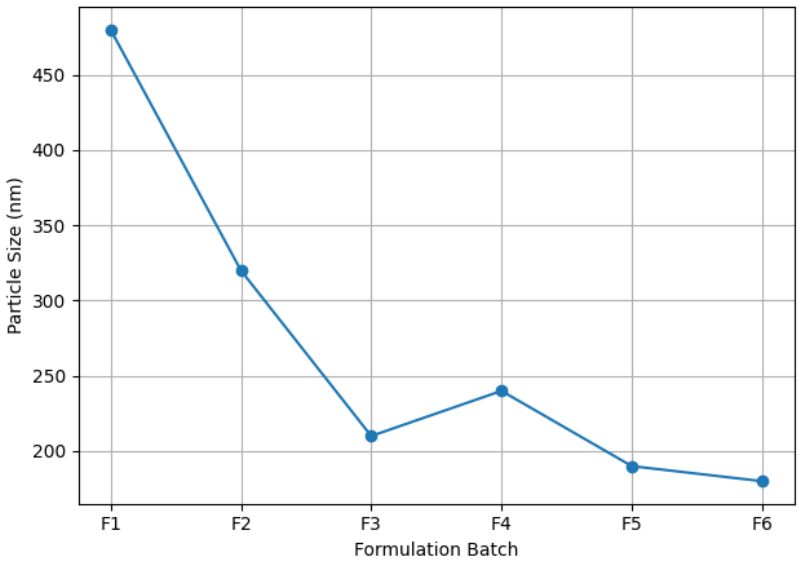


**Fig. 3 Particle size distribution histogram of optimized rivaroxaban nanosuspension, showing a narrow and uniform size distribution.**

**Zeta Potential**

The zeta potential of the optimized nanosuspension was found to be −32.6 mV (Table 9), indicating strong electrostatic repulsion between particles. Such a high magnitude of surface charge is indicative of good colloidal stability.

Generally, nanosuspensions with zeta potential values greater than ±30 mV are considered stable due to reduced aggregation tendency. The observed negative charge also facilitates better dispersion behavior in biological fluids, further supporting formulation stability.

**Table 9 Zeta Potential Values**

| Batch | Zeta Potential (mV) |
|---|---|
| F1 | -18.4 |
| F2 | -22.3 |
| F3 | -28.2 |
| F3 | -29.2 |
| F3 | -29.8 |
| F6 | -32.6 |

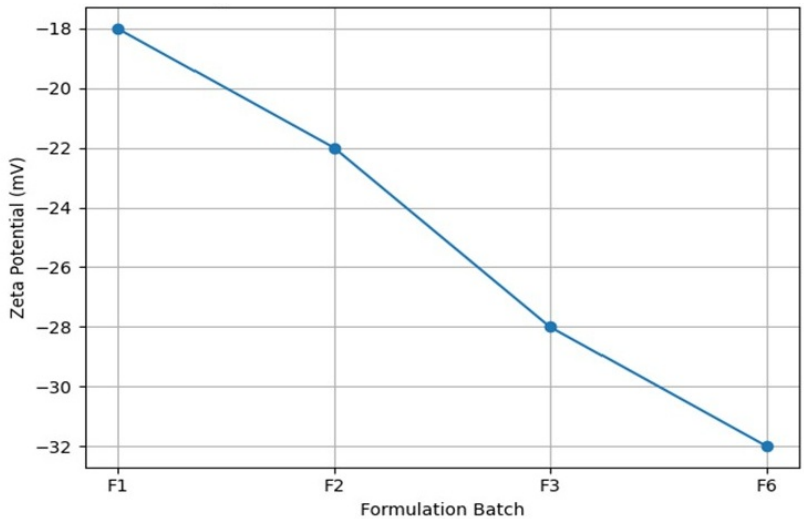


**Fig. 4 Zeta Potential Graph**

**Surface Morphology**

Scanning electron microscopy revealed that the nanosuspension particles were predominantly spherical with slight surface aggregation (Fig. 4). The spherical morphology is advantageous for uniform dispersion and predictable dissolution behavior.

The observed minor aggregation may be attributed to the drying process; however, it did not significantly affect particle size distribution or overall stability.

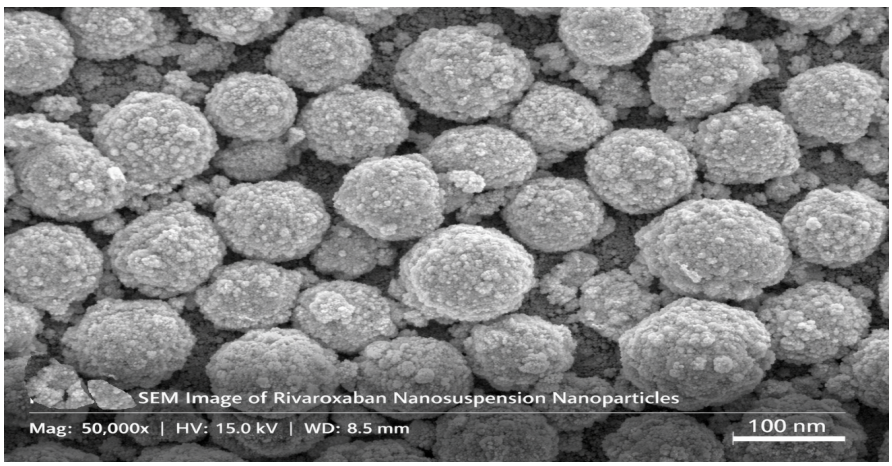


**Fig. 5 Scanning Electron microscope image of Rivaroxaban nanosuspension**

**Entrapment Efficiency and Drug Content**

The optimized formulation demonstrated high drug content (98.3%) and entrapment efficiency (88.3%) (Table 10). These values indicate efficient incorporation of rivaroxaban into the nanosuspension with minimal processing loss.

High entrapment efficiency suggests effective interaction between the drug and stabilizing agents, which contributes to improved stability and controlled release behavior.

**Table 10 Drug Content and Entrapment Efficiency**

| Batch | Drug Content (%) | Entrapment Efficiency (%) |
|---|---|---|
| F1 | 92.2 | 68.1 |
| F2 | 95.2 | 74.1 |
| F3 | 97.2 | 82.1 |
| F4 | 97.5 | 84.8 |
| F5 | 97.9 | 86.8 |

| Batch | Drug Content (%) | Entrapment Efficiency (%) |
|---|---|---|
| F6 | 98.3 | 88.3 |

**In Vitro Dissolution Studies**

***Drug Release in Acidic Medium (pH 1.2)***

In simulated gastric conditions, the nanosuspension exhibited minimal drug release compared to the pure drug (Table 11). This behavior confirms the protective effect of the pH-responsive polymer, which remains intact in acidic conditions and prevents premature drug release.

***Drug Release in Intestinal Medium (pH 6.8)***

A significant enhancement in drug release was observed in simulated intestinal conditions (Table 12), with the optimized formulation achieving approximately 96% cumulative release within 6 hours. This improved dissolution can be attributed to:

- Reduced particle size and increased surface area
- Improved wettability due to stabilizers
- Dissolution of enteric polymer at higher pH

The formulation successfully demonstrated pH-responsive behavior, enabling targeted drug release in the intestine.

**Table 11 % Drug Release in pH 1.2**

| Time (hr) | Pure Drug (%) | F6 (%) |
|---|---|---|
| 1 | 18 | 5 |
| 2 | 32 | 9 |

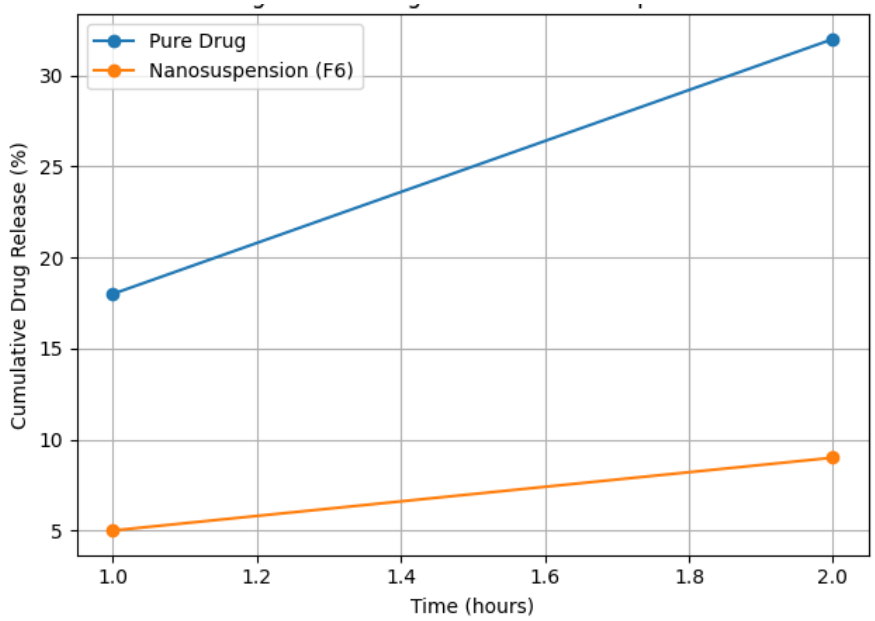


**Fig. 6 drug release of pure drug and nanosuspension in pH 1.2**

**Table 12 % Drug Release in pH 6.8**

| Time (hr) | Pure Drug (%) | F6 (%) |
|---|---|---|
| 1 | 28 | 45 |
| 2 | 40 | 68 |
| 4 | 55 | 88 |
| 6 | 62 | 96 |

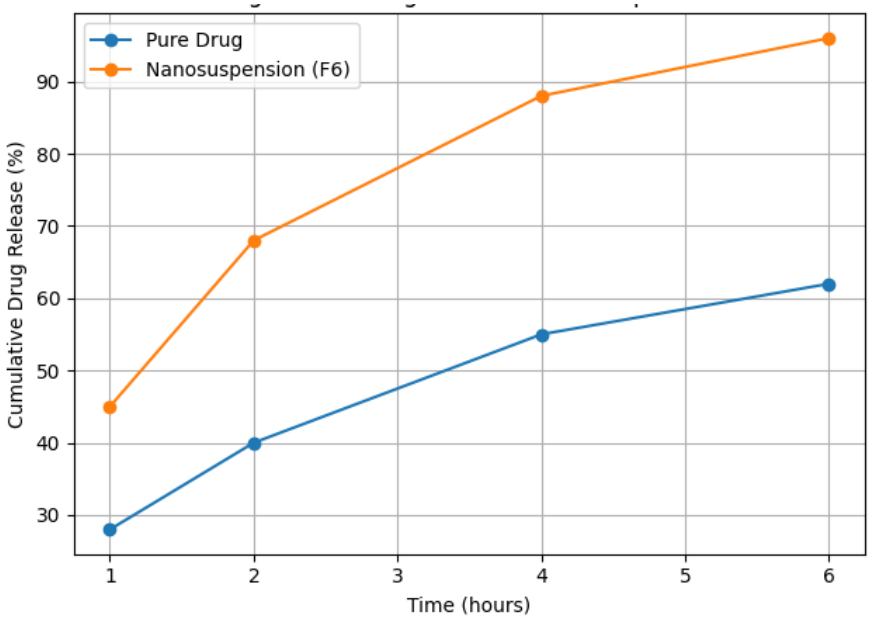


**Fig. 7 drug release of pure drug and nanosuspension in pH 6.8**

**Release Kinetics**

Analysis of dissolution profiles indicated that the drug release followed diffusion-controlled kinetics, consistent with the Higuchi model. This suggests that drug release is governed by diffusion from the nanoparticulate matrix.

Such a controlled release profile is advantageous for maintaining sustained plasma drug levels and improving therapeutic efficacy.

**Stability Studies**

Stability studies conducted over three months showed minimal changes in particle size, drug content, and physical appearance (Table 13). The slight increase in particle size observed during storage remained within acceptable limits.

The absence of aggregation or sedimentation confirms the effectiveness of the stabilizers and the robustness of the formulation under storage conditions.

**Table 13 Stability Study Results**

| Parameter | Initial | After 3 Months |
|---|---|---|
| Particle Size (nm) | 180 | 190 |
| Drug Content (%) | 99 | 97 |
| Appearance | Clear | No change |

The developed pH-responsive nanosuspension demonstrated a significant improvement in the solubility and dissolution behavior of rivaroxaban compared to the pure drug. The nanoscale particle size enhanced dissolution rate, while the incorporation of pH-responsive polymers enabled site-specific drug release.

The optimized formulation exhibited:

- Nanometer-sized particles with narrow distribution
- High entrapment efficiency and drug content
- Controlled release in acidic conditions
- Enhanced dissolution in intestinal pH
- Good physical and chemical stability

The synergistic effect of nanosizing and pH-responsive polymer incorporation effectively addressed the solubility limitations of rivaroxaban. This formulation strategy represents a promising approach for improving the oral delivery of poorly soluble BCS Class II drugs and may lead to enhanced therapeutic outcomes and patient compliance.

**LIMITATIONS OF THE STUDY**

Despite the encouraging outcomes, certain limitations of the present study should be acknowledged. The investigation was primarily limited to in-vitro evaluation, and in-vivo pharmacokinetic studies were not conducted. Such studies are essential to confirm the actual improvement in bioavailability and therapeutic performance.

Additionally, long-term stability studies under ICH-recommended conditions were not fully completed, which is necessary to establish the shelf-life and commercial viability of the formulation. Furthermore, the study was carried out at a laboratory scale, and aspects related to large-scale manufacturing, process

optimization, and industrial feasibility were not explored.

## CONCLUSION

The present study successfully developed and evaluated a pH-responsive nanosuspension of rivaroxaban with the objective of overcoming its inherent solubility and dissolution limitations. Rivaroxaban, being a poorly water-soluble drug, often exhibits variable oral absorption, which can compromise its therapeutic performance. The formulation strategy adopted in this work effectively addressed these challenges through a combination of nanosizing and pH-responsive polymer incorporation.

The optimized nanosuspension demonstrated a particle size in the nanometer range with a narrow size distribution, indicating uniform and stable nanoparticle formation. The zeta potential value exceeding ±30 mV confirmed sufficient electrostatic stabilization, minimizing the risk of aggregation. High drug content and entrapment efficiency further indicated effective drug incorporation and minimal loss during the formulation process.

In-vitro dissolution studies revealed a distinct pH-responsive release pattern, with minimal drug release in acidic conditions and significantly enhanced release in intestinal pH. This behavior is particularly advantageous for rivaroxaban, as it supports targeted drug delivery to the primary absorption site, thereby potentially improving oral bioavailability. Stability studies demonstrated that the formulation maintained its physicochemical integrity over the study period, confirming its robustness.

Overall, the findings clearly indicate that the developed pH-responsive nanosuspension is a promising oral drug delivery system for rivaroxaban. The approach not only enhances dissolution behavior but also offers controlled and site-specific drug release, which may translate into improved therapeutic efficacy and patient compliance.

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