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Formulation and Evaluation of Rivaroxaban-Loaded Sustained Release Nanosponges

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ABSTRACT:

This study reports the successful formulation of Rivaroxaban-loaded sustained-release nanosponges via the emulsion solvent evaporation method using ethyl cellulose as the polymer matrix, polyvinyl alcohol (PVA) as stabilizer, and glutaraldehyde as crosslinker. Ten formulations (F1–F10) were screened to optimize polymer concentrations, with the best batch showing 82.3% drug entrapment efficiency, a particle size of 247.50 nm, zeta potential of –33.4 mV, PDI of 0.249, and an 86.5% yield. In vitro release studies revealed 90.0% drug release over 24 hours, indicating effective sustained delivery. XRD confirmed reduced crystallinity of Rivaroxaban in the matrix, while TEM images showed uniform spherical nanosponges. Short-term stability at $40 \pm 2^\circ\text{C}$ / $75 \pm 5\%$ RH for 30 days showed minimal changes in entrapment efficiency and drug release, confirming formulation stability. These findings suggest that nanosponge-based delivery of Rivaroxaban offers a promising sustained-release platform to enhance patient compliance and therapeutic efficacy.

KEYWORDS: Rivaroxaban, Sustained Release, Nanosponges, Ethyl Cellulose, PVA, Entrapment Efficiency, Particle Size, Drug Release

INTRODUCTION

Thromboembolic disorders, including deep vein thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation-related stroke, are major causes of morbidity and mortality globally. Rivaroxaban, an orally active, selective direct Factor Xa inhibitor, has gained clinical significance due to its predictable pharmacokinetics and fixed dosing without the need for routine coagulation monitoring. However, Rivaroxaban's relatively short half-life (5–13 hours), low aqueous solubility, and pH-dependent bioavailability limit its sustained therapeutic effect, necessitating frequent dosing which may lead to poor patient compliance.[1-4]

To overcome these limitations, novel drug delivery systems are being explored to enhance its therapeutic potential. One such approach involves the development of nanosponges - a class of porous, nanoscale carriers capable of encapsulating both hydrophilic and lipophilic drugs. Nanosponges offer numerous advantages, including high drug loading capacity, protection of the encapsulated drug,

and controlled release characteristics. These carriers are typically composed of cross-linked polymers like ethyl cellulose, often stabilized using surfactants such as polyvinyl alcohol (PVA), and crosslinked with agents like glutaraldehyde to form a stable matrix.

Sustained release nanosponge formulations have demonstrated potential in reducing dosing frequency, improving drug bioavailability, and minimizing systemic side effects. By modulating the polymer-to-drug ratio, particle size, and surface charge, the drug release profile can be tailored to achieve a prolonged therapeutic effect. Previous studies with other anticoagulants and poorly soluble drugs have shown promising outcomes using similar nanocarrier platforms.[5-11]

In this study, we aim to formulate and evaluate Rivaroxaban-loaded sustained release nanosponges using the emulsion solvent evaporation technique. The effects of polymer concentration and stabilizer composition were systematically optimized. The resultant nanosponges were characterized for their physicochemical properties, in vitro

drug release behaviour, and short-term stability, with the goal of developing a stable, patient- friendly formulation that can improve the therapeutic performance of Rivaroxaban. [12-16]

Materials and Methods [7-9]

Materials

Rivaroxaban was gifted by Vanquest Pharma Private Limited Palghar, Ethyl Celulose, Poly Vinyl Alcohol, Glutaraldehyde 25%, Acetone and other ingredients used were analytical grade.

Pre-Formulation Study of Drug

- Morphological Evaluation of Rivaroxaban showed that the API was white crystalline odorless but bitter powder.

- Melting point of Rivaroxaban [18]

The open capillary method was used to measure the melting point of pure Rivaroxaban. The obtain melting point $232.66^{\circ}\text{C} \pm 0.510$ showed match with the reference melting point.

- Fourier-transform infrared spectroscopy (FTIR). [20]

FTIR spectroscopic analysis was carried out for pure drugs, polymers used, and their physical mixture for the compatibility evaluation of drugs and polymers. FTIR spectrophotometer (8400S, Shimadzu®, Kyoto, Japan) was used to obtain the spectra. The study showed that with all individual excipient the API maintained the functional group peak within the range and thus conform not any interation.

- Solubility Studies

The solubility of Rivaroxaban was evaluated in water, 0.1 N HCl, methanol, DMSO, acetone, and acetonitrile by vigorous shaking until a clear solution formed. Presence of undissolved particles was checked visually.

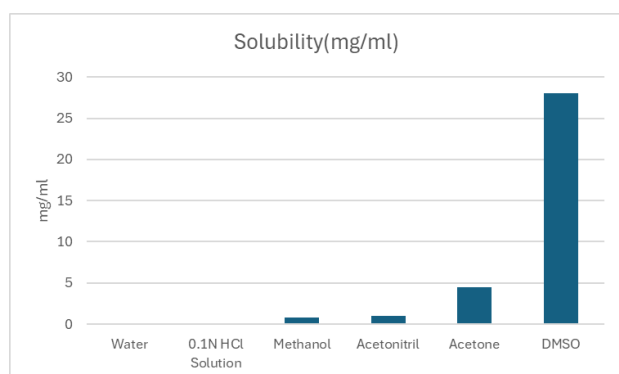


Figure 1 Solubility analysis

- Analytical method for estimation of Rivaroxaban: [17]

UV Spectroscopic Estimation in 0.1N HCl: A stock solution (1000 ppm) of Rivaroxaban was prepared in 0.1 N HCl. From this, serial dilutions (2–10 ppm) were made to construct a calibration curve using UV spectrophotometry. The method showed good linearity within this range.

UV Spectroscopic Estimation in DMSO: Similarly, Rivaroxaban was dissolved in DMSO to prepare a 1000 ppm stock solution. Serial dilutions (5–25 ppm) were used to generate a calibration curve. Linearity was observed across this concentration range.

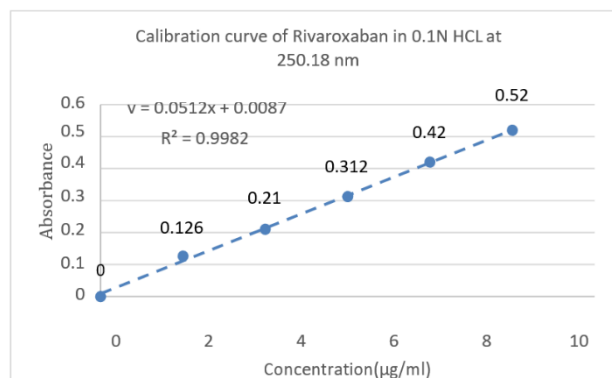


Figure 2 Standard curve of Rivaroxaban in 0.1 n HCL

Formulation of Nanosponges

Nanosponges were formulated using the emulsion solvent evaporation technique. Rivaroxaban (100 mg) and varying amounts of ethyl cellulose (300–500 mg) were dissolved in 25 mL of acetone to form the organic phase. Separately, a 0.5–1.5% w/v polyvinyl alcohol (PVA) solution was prepared in distilled water and used as the aqueous phase. Glutaraldehyde (1% v/v) was added as a crosslinking agent, pre-activated with 0.1 N HCl.

The organic phase was added dropwise into the aqueous phase under constant stirring (1000–1500 rpm), followed by ultrasonication for 10 minutes to promote nanosponge formation. Stirring continued for 4 hours to allow solvent evaporation. The nanosponges were then collected via centrifugation (4000 rpm, 15 minutes), washed with distilled water to remove unreacted materials, and dried in a hot air oven at 40°C for 12 hours.

Design of Experiment (DoE): 3² Factorial Design

A 3² full factorial design was employed to optimize the formulation of Rivaroxaban- loaded nanosponges using two independent variables-ethyl cellulose (X1) and PVA (X2)- at three levels (low -1, medium 0, high +1). The design generated nine trial formulations (F1–F9), assessing their effect on three dependent variables: entrapment efficiency

(Y1), zeta potential (Y2), and particle size (Y3). The polynomial model used:

$$Y = \beta_0 + \beta_1X_1 + \beta_2X_2 + \beta_{12}X_1X_2 + \beta_{11}X_1^2 + \beta_{22}X_2^2$$

Table 1 Evaluation of F1-F10 Batches

Batch Num.	%Entrapment Efficiency	% yield	Particle size (nm)	Zeta potential (mV)	PDI
F1	58.12	74.60%	234	-29.7	0.218
F2	66.54	78.30%	238	-30.9	0.244
F3	89.18	87.90%	259	-35.2	0.262
F4	84.43	86.10%	246	-34.4	0.258
F5	63.33	75.30%	220	-26.5	0.177
F6	72.17	81.50%	243	-31.6	0.243
F7	49.42	67.30%	212	-24.2	0.15
F8	57.45	70.10%	216	-25.7	0.166
F9	77.45	83.80%	242	-33.1	0.246
F10	62.78	77.50%	239	-31.8	0.24

Formulation of Factorial Batches

Ten formulations were prepared by varying EC and PVA ratios, while keeping Rivaroxaban (100 mg), glutaraldehyde (1% v/v), and acetone (25 mL) constant. A central point batch (F10) was added to validate reproducibility.

The optimized formulation (F11) was developed using Design-Expert-derived levels:

The formulation was prepared using standard procedures and subjected to evaluation for physicochemical parameters, reported in the Results section.

Evaluation of Nanosponges

- Drug Entrapment Efficiency

Entrapment efficiency (EE%) was determined by dispersing Rivaroxaban-loaded nanosponges (equivalent to 10 mg of drug) in 10 mL of DMSO. The dispersion was centrifuged at 4000 rpm for 30 minutes, and the supernatant containing the untrapped drug was analyzed using a UV-Visible spectrophotometer at 261.62 nm. The EE% was calculated using the formula:

$$\%Entrapment\ Efficiency = (\text{Weight of initial drug} - \text{weight of free drug}) / \text{Weight of initial drug} \times 100$$

- Percentage yield:

Use this formula to get the nanosponges yield in percentage terms. We measured the exact starting weight

of the ingredients and the finished weight of the nanosponge.

$$\%Percentage\ Yield\ (PY) = (\text{Practical mass of Nanosponges} \times 100) / \text{Theoretical mass (drug + Polymer)}$$

- Particle characterization:

At a temperature of 25 ± 1 °C, the Rivaroxaban Nanosponge's mean size and PDI were determined using a "Malvern particle size analyzer (Desla Nano C and Nano S, Beckman counter)". The optimal measuring angle for light scattering, which depends on the sample's concentration and scattering strength, is either set at 90 degrees to the incoming laser light or recorded as back scattering (173° - 177°). A transparent aqueous dispersion was achieved by reconstituting the correct amount of nanosponges in distilled water with sufficient dilution. To quantify particle size and PDI, the aqueous dispersion was sonicated for 10 minutes and then placed in a disposable clear plastic cuvette. With the exception of moving the aqueous dispersion into a glass electrode sample holder, the identical procedure was used to measure the zeta potential (ZP).

- Particle shape and morphology:

The Morphology of the Optimized Batch Nanosponges (NS11) was examined using TEM (FEI Philips Morgagni 268D). One drop of Formulation was put on a Carbon-covered copper grid and let to dry for Contrast enhancement.

- X-ray diffraction (XRD) analysis:

A study was conducted using X-ray diffraction (XRD) to assess the crystalline behaviour of both pure Rivaroxaban and an optimised Nanosponge (NS11) loaded with Rivaroxaban. The samples were examined using CuK α radiation that had been filtered with Ni ($\lambda = 1.5418$ Å), operating at 40 kV, 40 mA, with a receiving slit of 0.2 qinches, 2θ ranging from 5 to 75° C, and a scan rate of $0.040^\circ/s$. (X-Ray Diffractometer using Power X-Ray Analysis, Malveren P-analytical limited).

- In Vitro Drug Release Study:

The drug release profile of Rivaroxaban-loaded nanosponges was assessed using USP Apparatus II (paddle method) in 900 mL of 0.1 N HCl at 37 ± 0.5 °C and 50 RPM. Nanosponges equivalent to 15 mg of Rivaroxaban were filled into size 2 gelatin capsules and placed in the dissolution medium. Samples were withdrawn at specified intervals up to 24 hours and analyzed by UV

spectrophotometry at 250.18 nm. Cumulative percentage release was calculated, replacing each withdrawn volume with fresh medium to maintain sink conditions.

Stability of optimized batch:

The optimized Rivaroxaban-loaded nanosponge formulation was evaluated for short-term stability as per ICH Q1A (R2) guidelines. Capsules were stored at $40 \pm 2^\circ\text{C} / 75 \pm 5\% \text{RH}$ for 30 days in aluminium foil packs. Post-storage, samples were assessed for entrapment efficiency and 24-hour in vitro drug release in 0.1 N HCl. Results were compared to initial values to evaluate formulation stability under accelerated conditions.

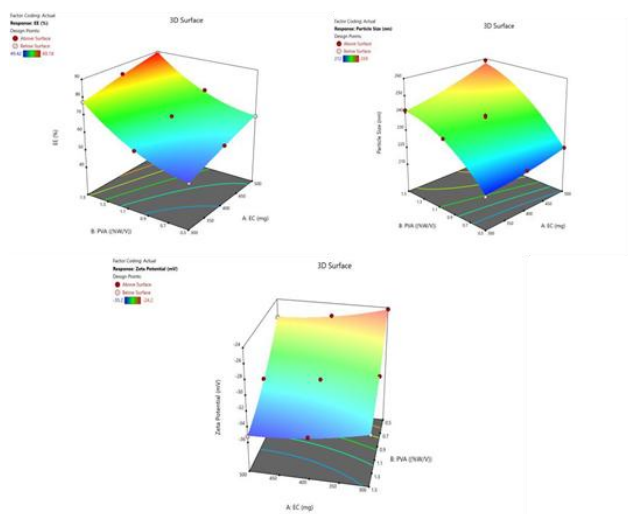


Figure 3 3D Graphical representation of the %EE, Particle Size and Zeta Potential

TEM analysis of Optimized Batch (F11)

The Diameter of Rivaroxaban Nanosponge was found to be in the range of 134-283 nm.

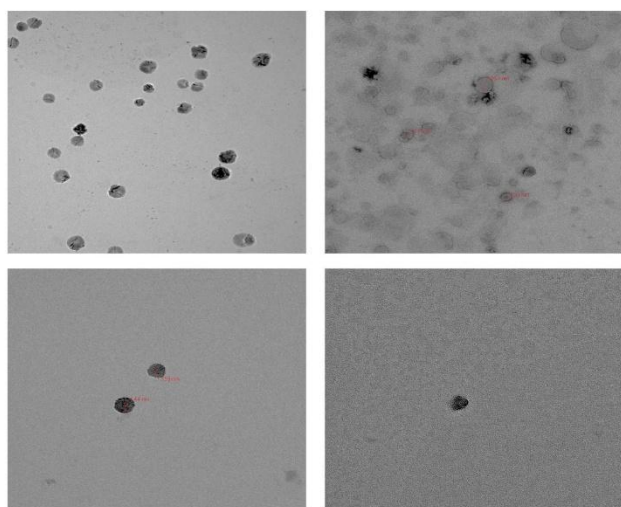


Figure 4 TEM Analysis of optimized Batch

XRD Analysis of Optimized Batch:

The X-ray diffraction (XRD) patterns of Rivaroxaban (RXB_DRUG) and Rivaroxaban-loaded nanosponge (RXB_NSP) were compared to analyze the crystalline characteristics of both substances.

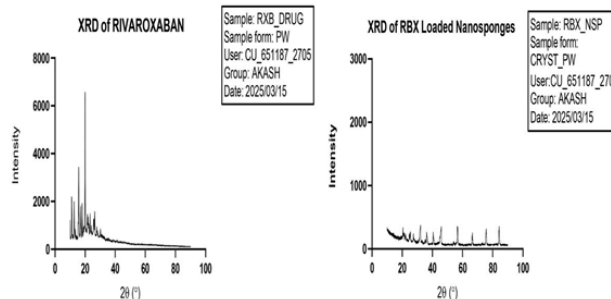


Figure 5 XRD Analysis of Optimized Batch

The XRD pattern of pure Rivaroxaban exhibited sharp peaks between 10° – 25° 2θ , with a prominent peak near 20° , confirming its crystalline nature. In contrast, the nanosponge formulation showed broader, less intense peaks, indicating reduced crystallinity and partial amorphization. This suggests successful molecular dispersion of Rivaroxaban within the nanosponge matrix.

Conclusion

Rivaroxaban-loaded sustained-release nanosponges were successfully developed using the emulsion solvent evaporation method, optimized for polymer and stabilizer concentrations. The optimized formulation exhibited high entrapment efficiency (82.3%), nanoscale particle size (247.5 nm), stable zeta potential (-33.4 mV), and uniform distribution (PDI 0.249). It achieved 90% drug release over 24 hours, with XRD and TEM analyses confirming reduced crystallinity and spherical morphology. Stability studies demonstrated minimal changes under accelerated conditions, confirming formulation robustness. These results support the potential of nanosponge-based systems to enhance Rivaroxaban’s oral delivery, sustain release, and improve patient compliance.

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