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Formulation and Characterization of Edoxaban-Loaded Solid Lipid Nanoparticles

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ABSTRACT

To produce solid lipid nanoparticles of Edoxaban to increase pharmacokinetics and anticoagulant efficacy in rats. Edoxaban-loaded solid lipid nanoparticles were optimized using the central composite architecture. Particle size and %EE were dependent factors, whereas medication, lipid, and surfactant concentrations were independent variables. The optimized Edo-SLN projected particle size, %EE, and PDI values, which matched the actual values. DSC findings validated the drug's amorphous state in the optimized Edo-SLN, whereas TEM data revealed nanodispersion and spherical particle shape. Drug burst and sustained release were seen in the formulations. Pharmacokinetic studies demonstrated that optimized Edoxaban formulations had higher bioavailability than simple drug solution. Better body weight and lower fasting blood glucose were seen with optimized Edo-SLN than with standard medication suspension. Edoxaban-loaded SLN were effectively synthesized and managed anticoagulant activity well. Data suggests SLN may improve Edoxaban bioavailability for anticoagulant treatment. They lower dose frequency compared to traditional dosage forms, improving patient compliance. These may be used to reduce blood clotting in the future..

Keywords: *Formulation, Characterization, Solid Lipid Nanoparticles, Anticoagulant Drug and Edoxaban.*

1. INTRODUCTION

Nanotechnology and nanomaterials are essential to new scientific and technological fields and have the potential to significantly and broadly affect the world economy and because of their many benefits, solid lipid nanoparticles (SLNs) have the potential to be drugs carriers. Because lipid carriers have a wide range of compositions and topologies, their physicochemical stability varies greatly. To fully characterize SLNs, appropriate analytical techniques are needed.

Size of SLN is 10–1000 nm. They are produced using both nature polymers, making them perfect for maximizing drug distribution and lowering toxicity [1,2,3]. The ability of nanoparticles to cross many anatomical barriers, continually discharge their contents, and maintain stability at the nanoscale sizes are all necessary for their successful use in medication delivery [4,5]. A solid lipid core and a cationic lipid surface that can attach to negatively charged DNA make up SLNs, a kind of particle carrier system [6].

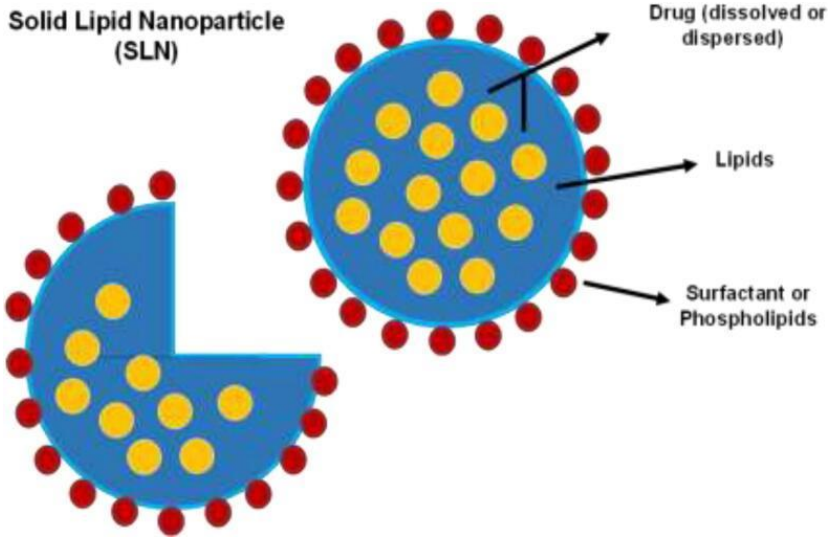

Fig. 1. The SLNs structure

Fatty acids make up SLNs, which are colloidal transporters that stay solid between 25 °C and 37 °C, the average body temperature. SLNs exhibit unique characteristics and many advantages over traditional formulations. Fig. 1 depicts the composition and organization of SLNs. Waxes are among the solid lipids used to create SLNs. Steroid fatty acids and triglycerides. SLNs between 50 and 1000 nm have been widely regarded as beneficial for the oral medication delivery of several active compounds. Additionally, SLNs produced using generally accepted safe ingredients are more compatible with the body, readily decompose, show less toxicity to animal cells, and are completely cooperative when employed for medication delivery. In order to create a fat medium in which medications or active ingredients might be condensed, SLNs are the first generation of a band of lipid nanoparticles made of solid lipids. Recently, surface modification and biopolymer coating have been used to improve the absorption degree and boost the effectiveness of SLN distribution. Preparations of SLNs offer better chemical stability of drug molecules and regulated drug release characteristics [7,8].

2. MATERIAL AND METHODOLOGY

Edoxaban was purchased from Sanat pharmaceuticals, New Delhi. Glycerol monostearate, Disodium Hydrogen Phosphate, Glyceryl Monooleate (GMO), Potassium dihydrogen phosphate, tween 80, n-octanol, methanol, etc. procured from Meerut Institute of Engineering and Technology, Meerut India.

2.1 Preformulation Studies

2.1.1 EDX Solubility in different solvents

The solubility of EDX is to be determined in different organic solvents like water methanol (MeOH), and phosphate buffer pH 6.8 by using the vial method. In this, a drug was taken in 10ml glass vials containing a 2ml solvent system and shaken manually till saturated followed by some drug being added in excess. The vial containing the saturated solution of the drug was kept in a mechanical shaker for 24hrs at 37º C. After 24hrs, the vial containing the drug solvent was removed and centrifuged at 10000 rpm for 20 min. to separate undissolved solids. After being extracted and suitably diluted, the decanted liquid was examined at 290 nm using a double-beam ultraviolet spectrophotometer. Based on absorbance data, the concentration has been observed from a standard plot. Then, the concentration was multiplied by the dilution factor. The same procedure was applied in all the solvent systems separately [9].

2.1. 2 Drug Excipients Compatibility

These studies are an important parameter of pre-formulation studies. Compatibility of EDX with selected lipids was determined by visual interactions (changes due to physical instability like color, conversion of physical state and odor, etc.) and physicochemical interaction [10].

2.1.3 Physical Compatibility

The drug and the drug with the excipients underwent physical compatibility testing for three weeks, the samples were stored at accelerated temperatures of 4°C and 25°C with 60% relative humidity. After mixing the drug and excipients until a saturated solution was achieved, the mixture was separated into six equal parts, three of which were sealed in vials and stored at various temperatures and relative humidity levels. Changes in color, texture, and physical appearance were examined in the samples [11].

2.1.4 Physicochemical Compatibility (FTIR)

Using an FTIR spectrophotometer (Agilent Technologies, Cary630), The drug, drug-loaded formulations, and the physical mixture (drug, lipids, and surfactants) all had their FTIR (Fourier transform infrared spectroscopy) spectra recorded. After positioning the sample on the diamond crystal knob and adjusting it to touch the sample, the sample was scanned between 4000-650 cm-1 using a 4 cm-1 solution [12].

2.2 Preparation of Edoxaban-Loaded Solid Lipid Nanoparticles through Experimental Design

A slightly modified version of a previously published approach was used to prepare the SLN. This method's lipid phase consisted of glyceryl monostearate and Edoxaban, while the aqueous phase was composed of tween 80, a non-ionic surfactant. They were both heated separately to 70ºC. A high-speed mechanical stirrer was used to gradually pour the aqueous phase into the mixture. lipid phase while keeping the at 70ºC. Stirring lasted for 30 minutes at 70ºC. Using a probe sonicator set to 40% amplitude for eight minutes, the produced emulsion's droplet size was decreased (Fig. 2). However, particle size rises as a result of particle aggregation when amplitude and time are increased beyond a certain point. Following sonication, the generated SLN were promptly kept at 4ºC [13].

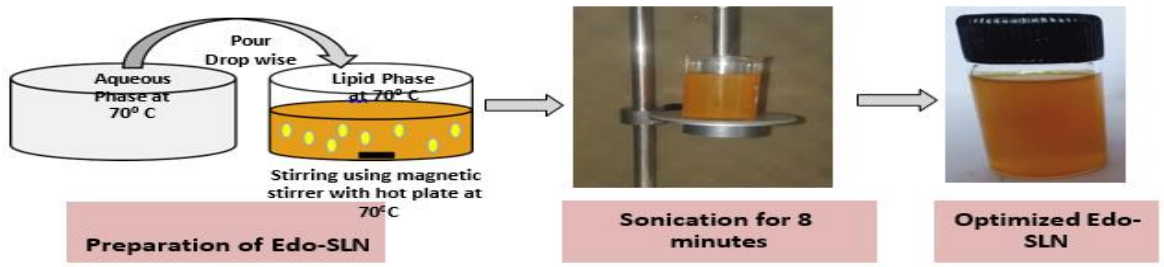

Fig. 2. Preparation of Edoxaban loaded SLN

2.3 Edo-SLN Characterization

2.3.1 PDI, and Zeta potential, Particle size

Distilled water was used to dilute the samples distilled water, and then the particle size, polydispersity index, and zeta potential of each formulation measured using the Malvern Zeta Sizer (Malvern, UK) [14].

2.3.2 Drug content

Using 10 milliliters of methanol to dilute 0.1 milliliters of SLN the drug content was ascertained. After two minutes of sonication, the mixture was strained via a 0.45 µm syringe filter. Spectrophotometric analysis of the fluid was performed at 421 nm. Formula for drug content [15].

2.3.3 % Entrapment efficiency

A cooling centrifuge was used to centrifuge one milliliter of prepared SLN at 4 degrees Celsius for forty-five minutes at 18,000 rpm. The quantity of unentrapped medicine in the supernatant was measured using a UV-visible spectrophotometer.

after it had been collected and diluted with a diluted buffer solution. The formula was used to determine the percentage entrapment efficiency [16,17].

$$\%\ Entrapment\ Efficiency = \frac{\text{Total drug content - unentrapped drug} \times 100}{\text{Total drug content}}$$

2.3.4 Morphological study

The morphology of the SLN was analyzed using a transmission electron microscope (TEM) with a negative stain (1% w/v phosphotungstic acid) was used to view the samples following the proper dilution using the preparation's original dispersion solution [18].

2.3.5 DSC study

The optimized SLN's DSC thermogram was acquired using the Perkin Elmer-DSC8000. To eliminate the water content, the improved SLN were freeze-dried. In the presence of a nitrogen environment, a tiny quantity (2–5 mg) of drug sample was heated while sealed in an aluminum pan to a temperature between 0 and 210°C (10°C per minute) [19].

2.3.6 FTIR Study

FTIR Study of the optimized formulation was conducted using the KBr pellet system by the FTIR spectrophotometer. Characteristic peaks in the 4000-650 cm-1 range were found in the absorption bands [20].

2.4 Stability Studies

The ICH (Q1A) criteria were followed for conducting stability studies. Following 180 days of storage at 25± 2ºC/60% ± 5% and 40ºC ± 2ºC/75% ± 5% temperature/relative humidity, the improved formulation was periodically examined for particle size, PDI, and percentage entrapment efficiency [21].

3. Result and Discussion

3.1. Pre formulation studies

3.1.1. Appearance: The Edoxaban is white colored and crystalline in nature.

3.1.2. Melting Point: The melting point of Edoxaban was observed at 177.5±0.325ºC when observed in triplicate and at 177.57ºC using a differential scanning calorimeter.

3.1.3. Solubility: The solubility profile data is shown in table 1. Edoxaban was practically insoluble in water and SGF pH 1.2 and very slightly soluble in simulated gastric fluid (SGF) pH 6.8 and simulated intestinal fluid (SIF) pH 7.4.

Table 1. Solubility studies of Edoxaban

Media	Solubility (mg/ml) ±SD	Term to be used
Water	0.085±0.006	Practically insoluble
SGF pH 1.2	0.0064±0.001	Practically insoluble
SIF pH 6.8	0.109±0.042	Very Slightly soluble
SIF pH 7.4	0.156±0.066	Very Slightly soluble

3.2. Identification of Drug

3.2.1. Fourier Transformation Infrared study

Edoxaban FTIR spectrum is displayed in Figure 3, and Table 2 provides an explanation of it. With distinctive peaks in the 4000-650 cm-1 range, the absorption bands were acquired. Edoxaban spectrum had the distinctive peaks of each functional group, which were discovered to correlate with the reference value and validate the medications' legitimacy.

Table 2. FTIR interpretation of Edoxaban

Sr. No.	IR absorption bands (cm-1)	Reference Value	Interpretation
1.	3503.30	3505	OH, stretching of phenol group
2.	1624.75	1625	C=O, C=C stretching
3.	1557.90	1600	C=C stretching of aromatic
4.	1152.80	1150	C–O–C asymmetrical stretching
5.	1273.20	1273	CH in plane bending
			of C=CH, aromatic
			C–O stretching
6.	719.88	713	C stretching

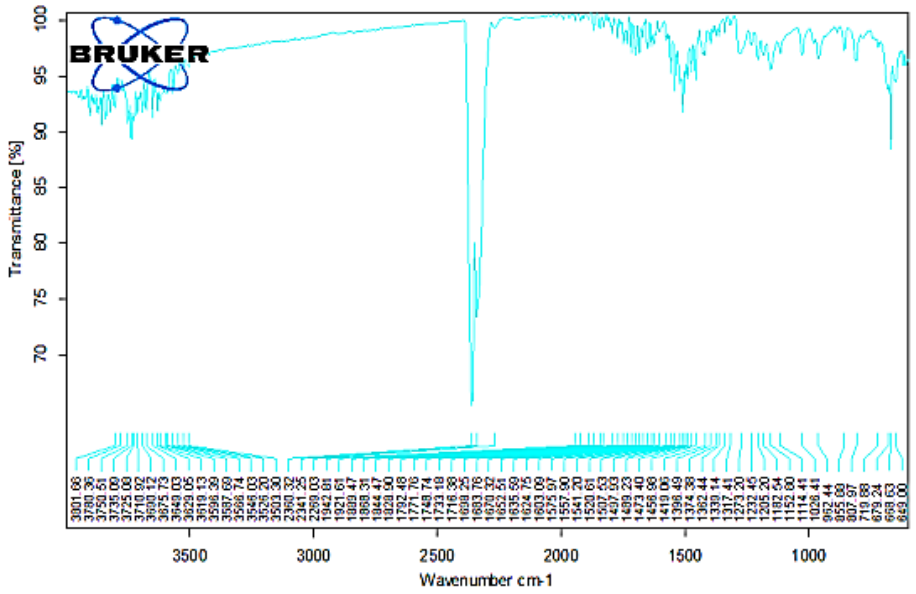

Fig. 3. FTIR spectra of Edoxaban

3.2.2. Differential Scanning Calorimetric Study

As seen in Figure 4, The DSC curve of Edoxaban give a prominent endothermic peak at 177.57ºC, with an enthalpy of 376.4 J/g. The drug's legitimacy is guaranteed by the DSC thermogram of Edoxaban, which verified the drug's crystalline nature and revealed that its melting point correlated with values published in the literature.

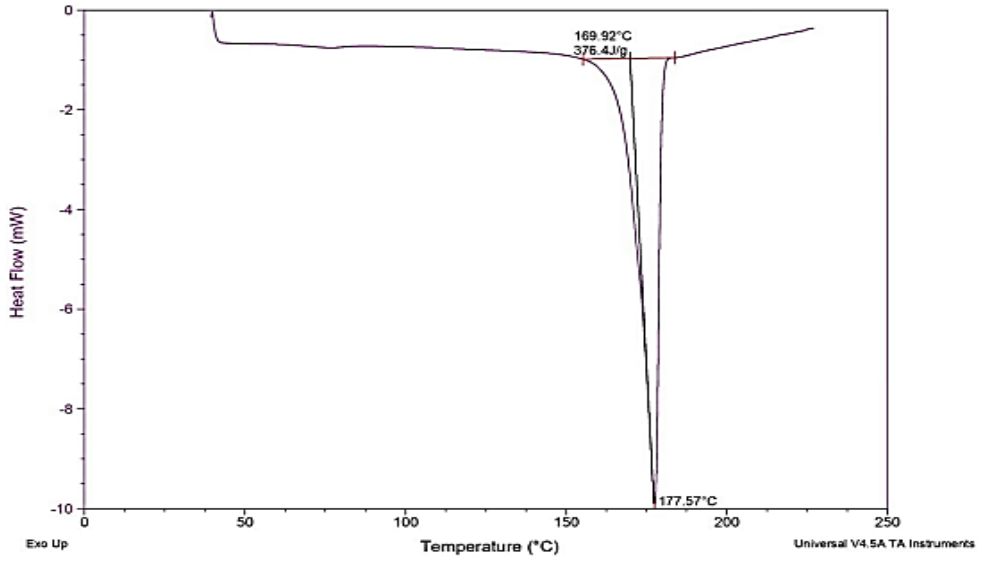

Fig. 4. DSC thermogram of Edoxaban

3.3. Characterization of Edoxaban loaded solid lipid nanoparticles using experimental design

Central composite design was used because to optimize the formulation variables. The independent factors selected for the study the concentration of drug, lipid and surfactant, each tested at three different levels: low, medium, and high. Emulsification and sonication were used to successfully create all of the formulations.

3.3.1. Analysis of Particle size

Table 3 displays the particle size and percentage entrapment efficiency for each formulation.

Table 3. Values obtained for particle size and % entrapment efficiency by conducting experimental runs (Edo-SLN)

Formulation		Particle Size (nm),	% Entrapment efficiency*
Run	code	Response Y1	Response Y2
1	F1	230.8	68.1±0.975
2	F2	118	56.9±1.282
3	F3	145	82.3±0.969
4	F4	238.8	93.5±0.827
5	F5	145.1	82.4±1.164
6	F6	95.21	68.4±0.993
7	F7	129.9	65±1.179
8	F8	362.7	85.1±0.938
9	F9	289.1	89.3±0.941
10	F10	145.7	82.4±1.172
11	F11	135.3	82.1±1.206
12	F12	322.6	93.7±0.893
13	F13	103.9	84±1.211
14	F14	145	82±1.308
15	F15	146.4	55.9±1.276
16	F16	239.7	65.2c0.985
17	F17	371.8	95.7±0.929
18	F18	130.7	61.8±0.958

*Values are expressed as Mean ± S.D.

Counter surface plots and 3D response surface plots were used to visualize the response surface analysis of the factors and outcomes. For each response, the sequential model sum of squares indicated that a quadratic model was the best fit, based on the highest-order polynomial. The regression coefficients for these quadratic equations were determined using the experimental data. The data for both responses were analyzed statistically through ANOVA, and the results are presented in Table 4.

Table 4. Statistical analysis using ANOVA (Edo-SLN)

Parameters	Particle size	% Entrapment efficiency
Coeff. Variation %	8.27	4.06
R^2	0.9850	0.9720
Adjusted R^2	0.9682	0.9404
Predicted R^2	0.8864	0.7871
Adequate. Precision	25.4082	19.1398

3.3.2. Zeta potential and PDI

The zeta potential, which varied from -17.3 to -25.2, showed how stable the formulation was (Table 5). The optimized batch's zeta potential is shown in Figure 5. It was discovered that raising the surfactant concentration reduced PDI. Conversely, the PDI rises as the medication and lipid concentrations do.

Table 5. PDI and zeta potential for each formulation (Edo-SLN)

Formulation	code	PDI	Zeta potential (mV)
1	F1	0.071	-17.3
2	F2	0.168	-21.1
3	F3	0.072	-17.9
4	F4	0.071	-23.9
5	F5	0.072	-17.6
6	F6	0.282	-14.8
7	F7	0.325	-22.1
8	F8	0.167	-25.2
9	F9	0.077	-24.4
10	F10	0.073	-17.9
11	F11	0.069	-17.4
12	F12	0.247	-21.0
13	F13	0.180	-18.2
14	F14	0.265	-17.6
15	F15	0.170	-22.4
16	F16	0.308	-23.5
17	F17	0.179	-16.2
18	F18	0.064	-23.7

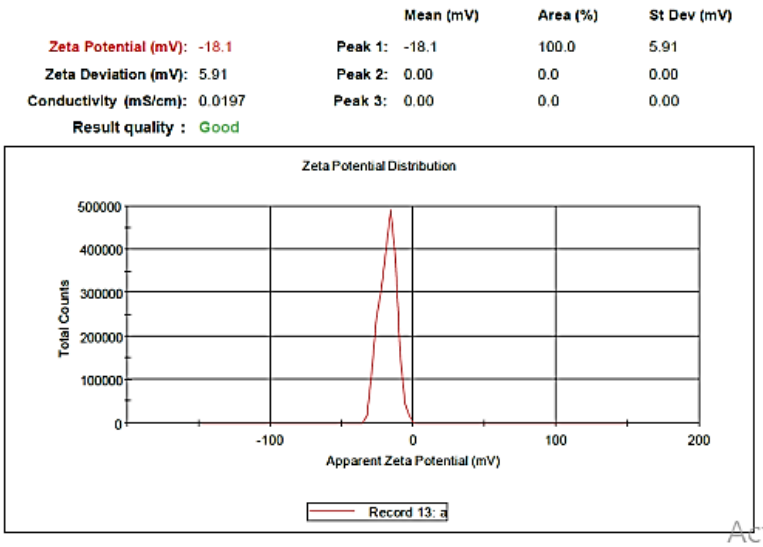

Fig. 5. Zeta potential for Edo-SLN optimization

3.3.3. In-vitro release study

The drug release trial lasted for twenty-four hours. In a 24-hour period, 79.81% of the medication was released by the simple drug suspension. By contrast, there was a 20% burst release of the drug during two hours. Then the formulation was refined, there was a steady release of up to 65.78% over the course of 24 hours. (Figure 6).

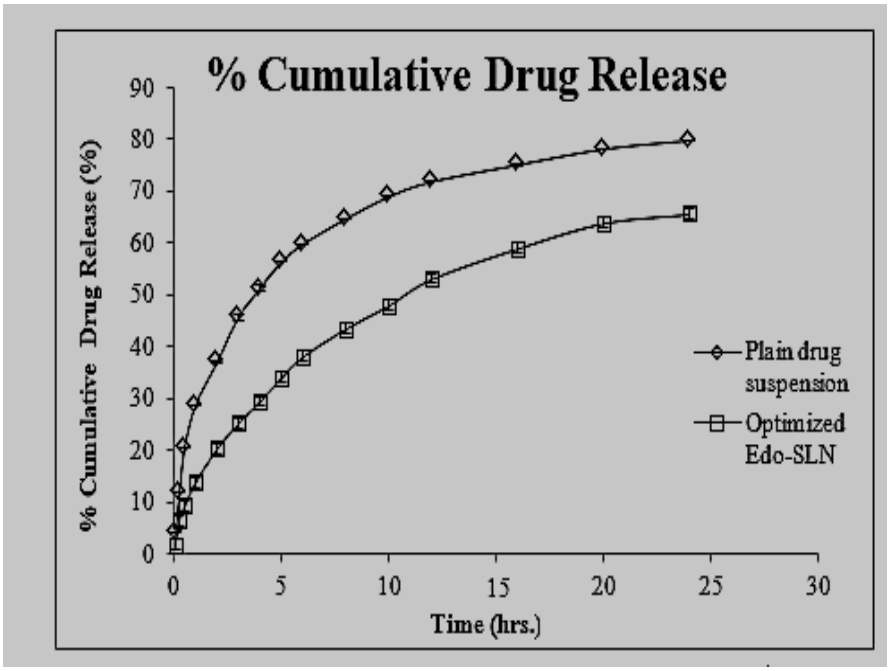

Fig. 6. In-vitro release of free drug and optimized Edo-SLN

3.3.4. Drug release kinetics

The Korsmeyer peppas model (figure 10), Zero-order (figure 7), First-order (figure 8), and Higuchi kinetics (figure 9) were all fitted to the in-vitro drug release data. The Higuchi model had the highest correlation coefficient value (R2 = 0.9895), demonstrating that the improved batch's release kinetics matched the Higuchi model.

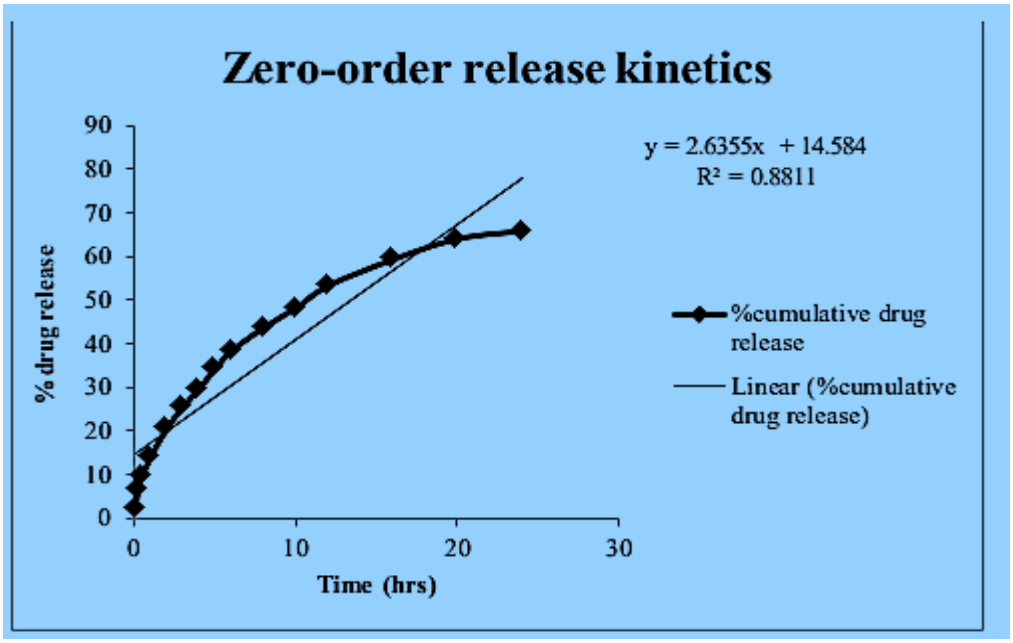

Fig. 7. Zero-order release kinetics for optimized Edo-SLN

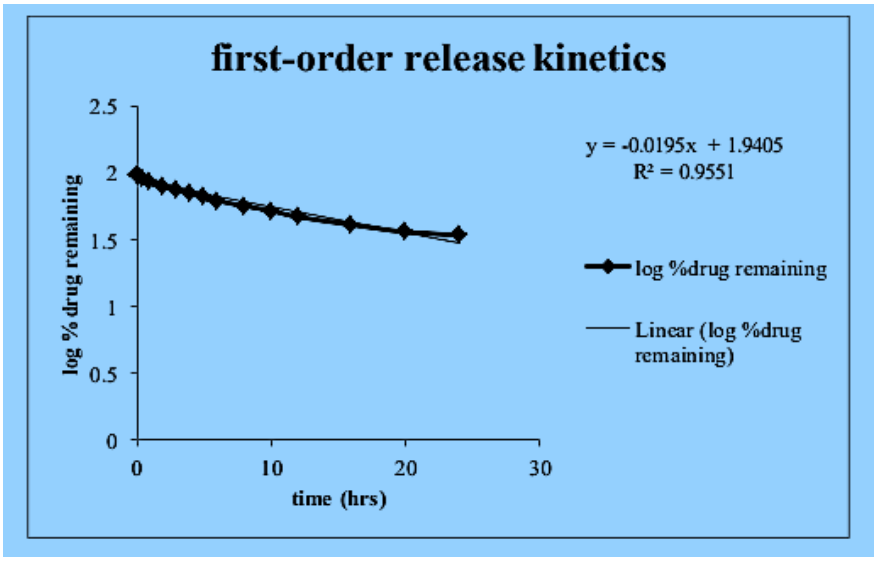

Fig. 8. First-order release kinetics of optimized Edo-SLN

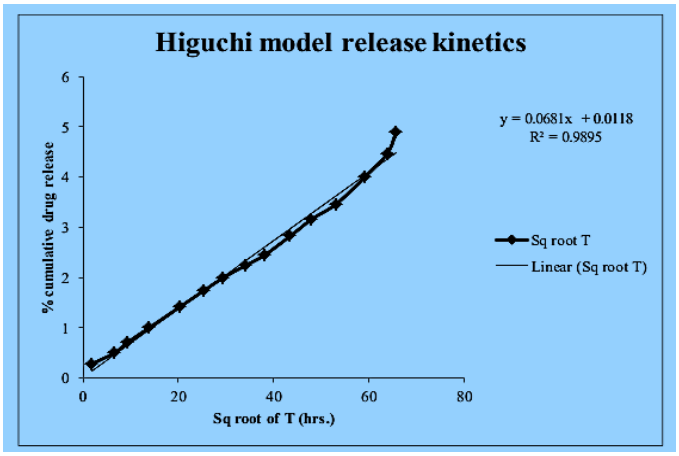

Fig. 9. Higuchi model release kinetics of optimized Edo-SLN

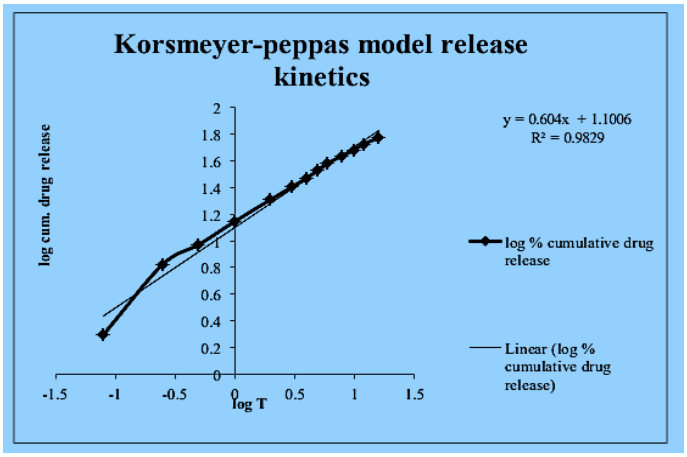

Fig. 10. Korsmeyer-peppas model release kinetics of optimized Edo-SLN

3.3.5. Morphological study

The particles were discovered to be monodispersed and spherical, with an average size of 120 nm (Figure. 11).

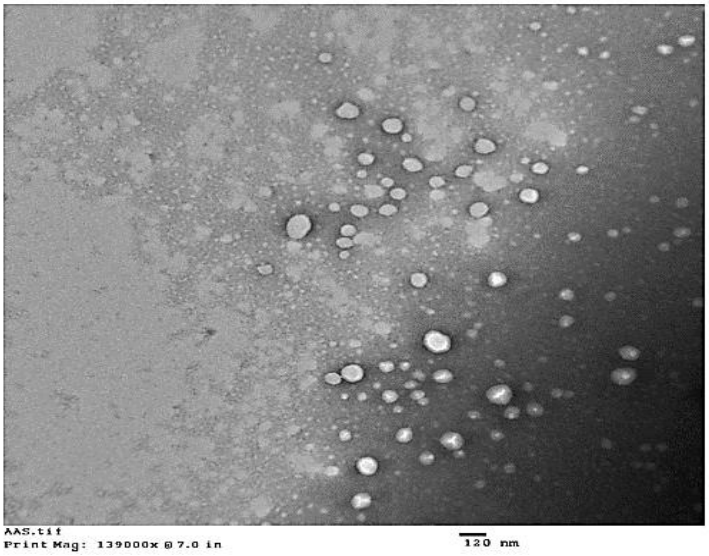

Fig. 11. Tranmission electron microscopy image of optimized Edo-SLN

3.3.6. DSC studies

The DSC thermogram of optimized Edo-SLN is shown in figure 12. The exothermic peak of glyceryl monostearate was observed while the Edoxaban peak disappeared. The broadness in GMS peak and shifting from 59.97ºC (in bulk) to 58.89ºC (optimized Edo-SLN) considering the enthalpy energy change from 353.0 J/g to 137.06 J/g was observed in DSC thermogram of optimized Edo-SLN.

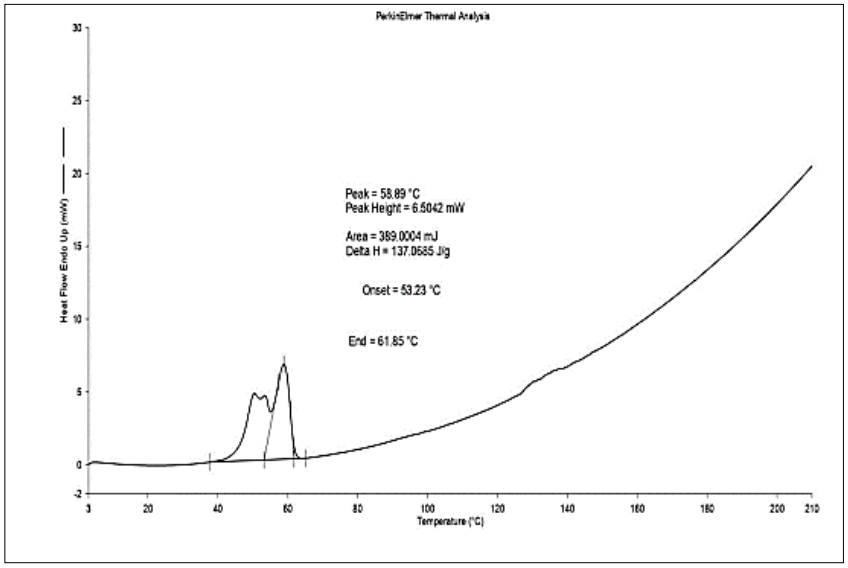

Fig. 12. Graph for DSC Thermogram of optimized Edo-SLN

3.3.7. FTIR study

The absorption peaks were present for all the functional groups in the spectra of optimized Edo-SLN (figure 13). The interpretation is shown in table 6. The slight shifting was observed in C–O–C asymmetrical stretching, C=O, C=C stretching of the drug, but they were still in the range specified in the IR chart.

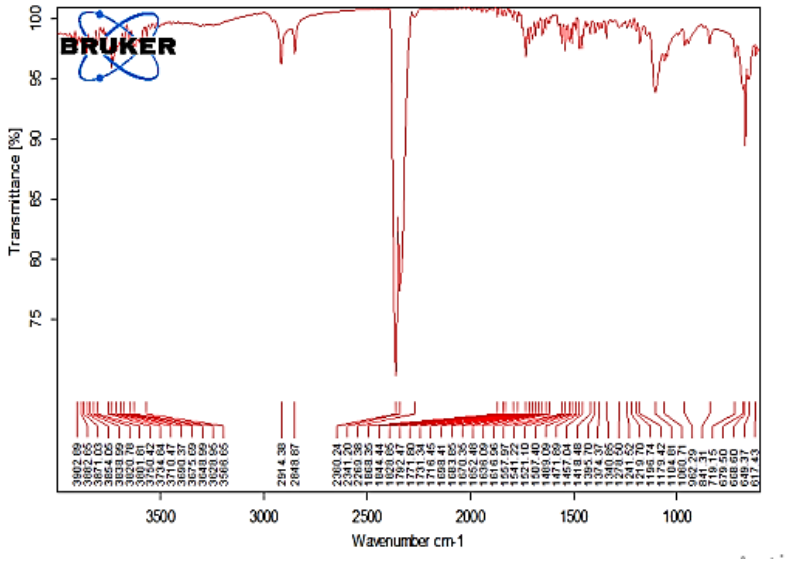

Fig. 13. FTIR spectra of optimized Edo-SLN

Table 6. FTIR interpretation of optimized Edo-SLN

Sr. No.	IR absorption bands (cm-1)	Physical Mixture	Optimized Edo-SLN	Interpretation
1.	3503.30	3503.06	3566.65	OH, stretching of phenol group
2.	1624.75	1623.67	1636.09	C=O, C=C stretching
3.	1732.66	1732.15	1731.34	C=O stretching of ester
4.	1557.90	1557.93	1557.97	C=C stretching of aromatic
5.	1152.80	1176.93	1179.42	C–O–C asymmetrical stretching
6.	1273.20	1265.88	1278.50	C-H in plane bending of C=CH, aromatic C–O Stretching
7.	719.88	717.97	719.15	C stretching
8.	2917.34	2913.30	2914.38	CH3 stretching of alkane
9.	2850.79	2848.54	2848.87	CH2 stretching of alkane

3.4. Pharmacokinetic studies

Compares the oral administration pharmacokinetics of the optimized Edo-SLN and simple drug solution with figure 14. Plasma concentration versus time profile was used to compute a number of pharmacokinetics parameters, including Cmax, t max, AUC, Kel, t1/2, Vd, and Cl; the findings are displayed in Table 7. When comparing the t max and half-life of the improved Edo-SLN to a plain drug suspension, a significant difference was found. With a p-value that was highly significant, the optimized formulation's volume of distribution (Vd) and clearance were lower than those of the simple drug suspension. It was discovered that the improved Edo-SLN's plasma drug concentration/time curve yielded Cmax and AUC (0-24) that were 5.21 and 7.34 times higher ($p<0.01$) than the suspension of drug. The relative bioavailability (F) of optimized Edo-SLN was found 734 %.

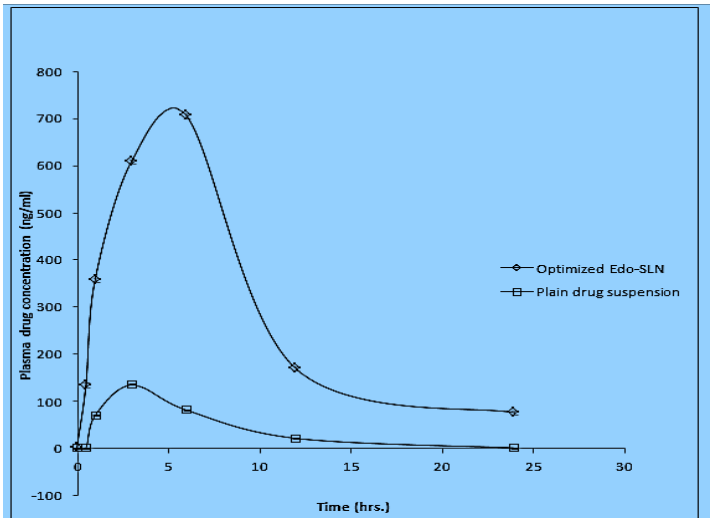

Fig. 14. Comparison of the pharmacokinetics of optimized Edo-SLN and plane suspension of drug

Table 7. Comparative results of pharmacokinetics parameters of optimized Edo-SLN and plain suspension of drug

Pharmacokinetic parameter	Optimized Edo-SLN*	Plain drug suspension*
Cmax) (ng/ml)	704.43±49.98***	135.35±24.17
AUC (0-t) (ng/ml*h)	7165.70±313.25***	975.606±119.18
AUC (0-inf) (ng/ml*h)	8376.123±392.3***	1155.055±168.83
Tmax (hrs.)	6±0.00	3±0.00
Kel (h-1)	0.06196±0.003	0.115±0.001
T1/2 (hrs.)	11.18±1.91**	6.01±1.33
Vd (L)	245.24±18.77***	748.96±44.89
Cl (L/h)	15.19±3.15***	86.22±6.54
F	734%	-

***Values are expressed as Mean±SD. **Unpaired T-test, and ***p**

3.5. Stability Studies

The data for the six-month stability studies are shown in Table 8. The EDO-SLN's physical characteristics were unchanged during this time, However, under both temperature conditions, the percentage of entrapment efficiency slightly dropped.

Following 180 days of storage, the optimum formulation particle size increased from 119.7 to 120.8 nm at 25ºC ± 2ºC/60% ± 5% RH and from 119.7 to 125.9 nm at accelerated circumstances; the results are in correlation with the study.

Table 8. Stability profile of optimized EDO-SLN over six months

25ºC ± 2ºC/60% ± 5% RH					40ºC ± 2ºC/75% ± 5% RH		
Sr. No.	Days	Physical Appearance	Entrapment Efficiency ± SD (%)*	Particle Size (nm)	Physical Appearance	Entrapment Efficiency ± SD (%)*	Particle Size (nm)

1.	0	Yellowish-color suspension	81.93±0.974	119.7	Yellowish-color suspension	81.93±0.974	119.7
2.	30		81.67±1.65	119.7		80.95±1.78	119.9
3.	60		81.20±1.12	120.2		79.60±1.45	120.6
4.	90		80.88±1.32	120.2		79.35±1.63	123.4
5.	180		80.45±1.72	120.8		78.93±1.22	125.9

4. Summary and Conclusion

Through heat homogenisation was succeeded by ultrasonication method. The pre-formulation investigations of the medication were conducted, and the results facilitated the selection of an appropriate solvent for the formulation process. The excipient ranges were determined based on the outcomes of first testing. The FTIR spectra revealed that the medication and its preparations exhibit analogous distinctive peaks. Consequently, it may be concluded that the medication and the excipients utilized did not interact chemically. Seven formulations were made and evaluated based on studies on in vitro drug release, particle size, and entrapment efficiency. The optimal formulation must have continuous drug release, tiny particle size, and maximum entrapment efficiency. With an entrapment efficiency of 74.86±1.9%, a particle size of 231.1±3.1 nm, a zeta potential of -22.3±0.13 mV, and an in-vitro drug release of 72.74±0.31, F3 was determined to be the optimal formulation. SEM was used to analyze the optimized formulation's surface morphology. DSC was used to determine the formulation's and the pure medication's melting points. When compared to the release of the pure medication, the improved formulation's in-vitro trials show controlled drug release. Results indicate that drug release adheres to Higuchi's model, which is indicative of regulated drug release. Consequently, the SLNs provide an innovative method for enhancing the oral bioavailability of EDO.

Abbreviations

EE	Entrapment Efficiency
PDI	Polydispersity index
Edo-SLN	Edoxaban Solid lipid nanoparticles
LDC	Low loading capacity
FTIR	Fourier Transform Infrared
UV	Ultraviolet
ICH	International Conference on Harmonization
SGF	Simulated gastric fluid
SIF	Simulated intestinal fluid

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