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Development Optimization and Evaluation of Lipid-Based Nanoparticles of Apixaban by Melt Emulsification Method

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Abstract

Apixaban is a US FDA-approved molecule recommended for stroke prevention, thromboembolism, deep vein thrombosis, and pulmonary embolism. The elevated lipophilicity and poor bioavailability of Apixaban restricted their therapeutic efficacy. The present research focused on the advances of solid lipid nanoparticles (SLN) of Apixaban for greater therapeutic efficacy and also to deliver sustained released action. The SLN was developed by the melt emulsification method. The compatibility of Apixaban was assessed with the lipids by FTIR and DSC. Among the several lipids, glyceryl monostearate was chosen as the best lipid and polyethylene glycol 200 as surfactant. The optimization of SLN was carried out by Box-Behnken design involving the concentration of lipid (X1), surfactant (X2), and sonication time (X3) as independent factors. The therapeutic efficacy of SLN was achieved through the particle size (Y1) and entrapment efficiency (Y2) as a dependent factor. The optimized batch F6 showed a particle size of 243.9 nm, zeta potential of -20.8 mV, and PDI value of 0.372. The drug entrapment efficiency was highest in F6 was 83.69 %. The in-vitro drug released showed sustained action for about 24 hours. The scanning electron microscopy confirmed the lyophilized powder in the nanoscale range (111.3 nm to 255.3 nm).

Keywords: Apixaban, Solid lipid nanoparticles, deep vein thrombosis, Box-Behnken design, Melt-emulsification method.

Introduction

The generation of an unwanted mass within the blood leads to the development of a condition termed thrombosis. Similarly, the same process occurred in the deep vein then it is known as deep vein thrombosis (DVT). DVT is a very critical condition that is unobservable and the progressive stage leads to the development of pulmonary embolism (PE) and pulmonary hypertension (PH) (1), (2). After the outbreak of COVID-19, the population in the entire world greatly suffered from cardiovascular diseases including DVT, PE, and PH (3).

Generally, the occurrence of DVT in the world is > 67 people in 1 lac population. The acute onset of pain, inflammation, redness, and erythema in the lower limbs are the characteristic features of DVT. The chances of recurrence of DVT are extremely high where conventional medicine is unsuitable. Hence, these situations are well-treated with the help of sustained-release formulations which minimizes the chances of mortality and morbidity (4).

Oral anticoagulant therapy is widely recommended by physicians and surgeons in the prevention of the conditions associated with DVT. Among these, Warfarin is a well-known medicament but also has several limitations such as bleeding, toxicity, and the extreme risk of drug–drug interactions (5). Hence, currently, direct oral anticoagulants are in huge demand which overcomes the drawback of warfarin. These are classified into direct Xa factor inhibitors (Apixaban) and direct thrombin inhibitors (Dabigatran). Among these, Apixaban is highly popular for the prevention and treatment of DVT, and PE due to their potency and safety concern (6).

Apixaban is a US FDA-approved molecule recommended for stroke prevention, thromboembolism, DVT, and PE. The patients treated for total hip replacements also suggested the oral administration of Apixaban having the chances of thrombosis. The versatile applications of Apixaban are restricted due to high lipophilicity and low bioavailability. Hence, the current research work focused on the improvement of bioavailability and providing the sustained action of Apixaban via SLN (7) (8).

The most widely utilized technique for the improvement of solubility and bioavailability of active pharmaceutical ingredients is lipid-based drug delivery. Among these, solid lipid nanoparticles (SLN) are the versatile nanocarrier system for offering higher physical stability, sustained or controlled release pattern, and high entrapment efficiency and applicable for the several routes of drug administration (9). The colloidal nanocarrier system composed of lipids in their solid state and surfactant for stabilization is known as SLN. These nanoparticles exist in the wide range of 50-300 nm. Moreover, the SLN is highly preferred over liposomes and polymeric nanoparticles for their safety and biocompatibility concerns as these systems does not utilize organic solvents. The formulation components of SLNs are solid lipids such as long chains of fatty acids, triglycerides, and waxes. The highly preferred lipids are glyceryl monostearate (GMS), glyceryl behenate (GBH), glyceryl stearate, etc. The emulsifiers incorporated for the stabilization of colloidal dispersions are non-ionic surfactants such as Poloxamer 188, Tween 80, Span 80, etc. (10metastatic cancer and the leading cause of mortality in females worldwide. The lack of expression of triple receptors namely, estrogen, progesterone, and human epidermal receptor2 defined TNBC. OBJECTIVE The current review introduced the novel biomarkers such as miRNA and family, PD1, EGFR, VEGF, TILs, P53, AR and PI3K, etc. contributed significantly to the prognosis and diagnosis of TNBC. Once diagnosed the utilization advanced approaches available for TNBC because of the limitations of chemotherapy. Novel approaches include lipid-based (liposomes, SLN, NLC, and SNEDDS) (11).

The formulation and evaluation of the SLN of Apixaban were performed with the help of the quality by design (QbD) approach. This process enabled the successful progress of the product with the minimal involvement of material and assessing the risk factors. The principle components of QbD for the progress of SLN comprised quality target profile (QTP), quality target product profile (QTPP), critical quality attributes (CQA), and critical material attributes (CMA) (12). The CQA for the SLNs are the particle size (PS), and the entrapment efficiency (EE).

Materials and Methods

Apixaban was supplied by Natco Pharma, Kothur, Telangana. The glyceryl monostearate (GMS), was received from Ajanta Pharma, Aurangabad. The glyceryl behenate was gifted by Gangwal Chemicals, Mumbai. All other materials utilized were of analytical grade only.

Scrutiny of lipids

The lipophilic actives are dissolved rapidly in the lipids; hence the selection of the best compatible lipid was the prime criterion for the development of SLN. At the initial stage, the

quantity of lipids was taken and the therapeutic dose of Apixaban was transferred to the melted lipid mass by heating them 5-10 ^{0} C above the melting point. The test tubes were placed on the vortex mixer and further diluted to analyze the solubility of Apixaban. The samples were scanned by the UV-visible spectrophotometer (UV-1900 Shimadzu) at 264 nm (13low oral bioavailability (<10%).

Selection of surfactant

The SLN is a colloidal dispersion hence, the solution was unstable. For the improved stability of the colloidal dispersion, the best suitable surfactant or stabilizer indicating the highest solubility was picked. The therapeutic dose of Apixaban was transferred into several test tubes containing Poloxamer 188, Tween 80, and Span 80 respectively. These test tubes were placed on the vortex mixer for about 10-15 min and samples were analyzed spectrophotometrically at 264 nm (14).

FTIR

The distinctiveness of Apixaban was carried out with FTIR (Shimadzu, Japan Iffinity-1s model). Likewise, the compatibility of Apixaban was tested with its components such as GMS by scanning the mixture between the ranges of 500-4000 cm^{-1} with a resolution of 2 cm^{-1} (15).

Differential scanning calorimetry (DSC)

The melting point and physical nature of the Apixaban-GMS loaded sample were evaluated with DSC (DSC, Mettler, Star SW13, UK) by heating the sample in the range of 50-300^{0} C under the inert nitrogen gas at the flowing rate of 40 ml/min. The Apixaban GMS thermogram was recorded (16).

Box-behnken design for the optimization of sln

The optimization analysis using the BBD involves 3-independent factors such as concentration of lipid (GMS-X1), surfactant (PEG 200-X2), and sonication time (X3). The therapeutic efficacy of SLN is dependent on the particle size (Y1) and the entrapment efficiency (Y2). The Design of Expert (Version 13 Stat-Ease) was utilized which predicted the 12 randomized runs for the development of SLN batches. Further, the ANOVA was applied and its interpretation was predicted (17) (18).

Preparation of SLN of apixaban

The preparation of SLN of Apixaban was performed by the melt-emulsification and ultrasonication methods. The BBD displayed 12 randomized trial runs for the formulation of SLN and consequently measured. The amounts mentioned in the BBD for GMS were weighed precisely and heated at a temperature of 65-70^{0} C so that the lipid was melted absolutely. The Apixaban was transferred into the molten mass of the GMS tube. Correspondingly, in another tube, Milli Q water (10 ml) was measured which was heated at a similar temperature and Tween 20 was added to it. The aqueous surfactant solution was added via a syringe in dropwise into the lipid phase and placed on the magnetic stirrer at 70^{0} C with a continuous speed of 3000 rpm (Remi, Instruments, Mumbai). The stirring was sustained until a clear transparent emulsion was developed which was further sonicated for probe sonicator to achieve the desired particle size of SLN-loaded Apixaban. The prepared SLN was packed cautiously and stored at a temperature of 4^{0} C (19) (20).

Evaluation of SLN

Determination of PS, PDI and ZP

The developed SLN of Apixaban was exposed to a particle size analyzer (Nano ZS Malvern, UK). The colloidal dispersion was diluted with double distilled water and analyzed by dynamic light scattering method (21).

Entrapment efficiency (EE)

The EE (%) for Apixaban was assessed by measuring the concentration of unentrapped drugs in the colloidal dispersion. The sample

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was centrifuged at 25, 000 rpm for 30 min to separate the supernatant solution. This solution was analyzed spectrophotometrically at 264 nm for the assessment of unentrapped active ingredients. The percentage of EE was calculated by using the following equation (22).

$$\% \text{ Entrapment efficiency} = \frac{\text{Quantity of entrapped drug}}{\text{Total quantity of drug}} \times 100$$

In-vitro dissolution studies

The in-vitro drug dissolution studies were performed with the dialysis bag method. The identified quantity of Apixaban-loaded SLN formulation was positioned in the bag and later in the USP type I dissolution apparatus. The dissolution apparatus was filled with 0.1 N HCl at 37^0 C and rotated at 50 rpm. The samples were withdrawn at regular intervals of 1h for about 12 h and replaced immediately with the fresh solution. Finally, the samples were analyzed with a UV-visible spectrophotometer at 255 nm (23).

Lyophilization of SLN

The colloidal dispersions have less stability from a physical and chemical point of view. Hence, the optimized batch of SLN was subjected to lyophilization and mixed with mannitol. The resultant mixture was kept in a deep freezer at -20^0 C and further lyophilized at -52^0 C at a pressure of 0.002 mbar for 48 h to get a lyophilized powder sample. The obtained sample was filled into the capsule for oral delivery (24).

Stability study

The optimized batch was subjected to stability testing kept at 25^0 C, and 60 % relative humidity in the packed Eppendorf tube. The samples were withdrawn at an interval of 1 month and analyzed for particle size and EE (25).

Results and Discussion

Scrutiny of lipids

The glyceryl monostearate (GMS), glyceryl behenate (GBH), glyceryl distearate (GDS) and stearic acid (SA) were shortlisted for the improvement of solubility of Apixaban. Among these lipids, the highest amount of Apixaban was dissolved in the GMS (39µg) followed by GDS (35µg), GBH (29µg), and SA (17µg). Hence, the highest solubility was observed in the GMS which was selected as the best lipid for the development of SLN of Apixaban.

Selection of surfactant

The surfactant or stabilizer was required for the good stability of the colloidal dispersion. Moreover, the surfactant minimizes the interfacial tension among the different phases. Among the several picked surfactants, the highest solubility and stability for the colloidal dispersion was observed in the polyethylene glycol 400. The Apixaban was completely dissolved in the PEG 400 and the solution remained clear and transparent. Whereas, in Tween 80, Span 80 and Poloxamer 188 dispersion, slight turbidity was observed.

FTIR

The powder material received was analyzed for the purity and identity of Apixaban by FTIR. The spectrum achieved was construed for the bands and the stretchings. The high-pitched peak was noted at 3743.83 cm^{-1}, and 3309.85 N-H cm^{-1} for N-H stretching, 2166.06 cm^{-1} observed for C-H stretching, 1625.99 cm^{-1}, and 1595.13 cm^{-1} for C=C stretching, and 1186.22 cm^{-1}, 1510.26 cm^{-1}, 1251.80 cm^{-1} for C=O stretching. The compatibility of Apixaban with GMS was confirmed by the FTIR. The FTIR spectrums were showed in Figure 1 and 2.

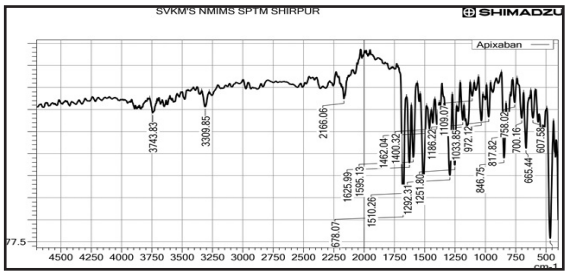

Figure.1: The FTIR spectra of Pure Apixaban

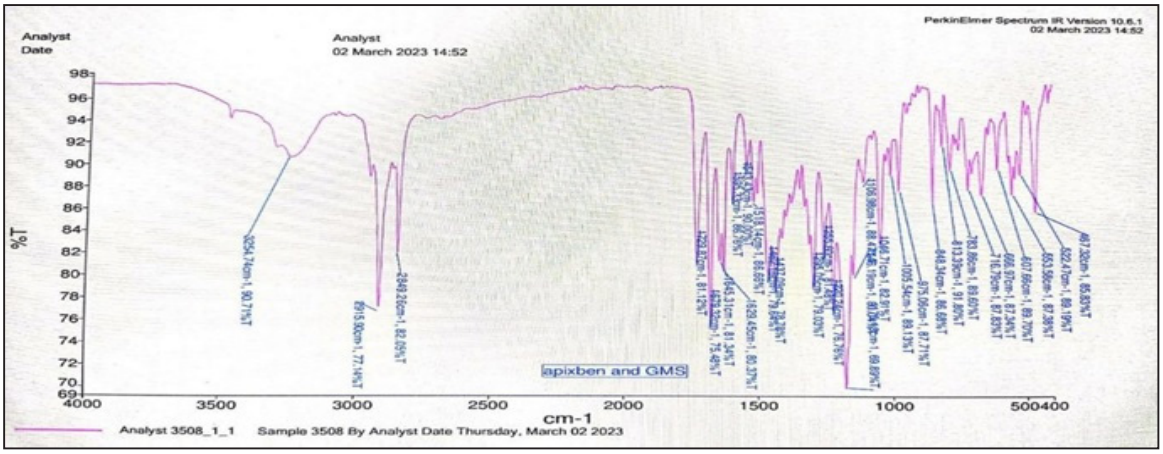

Figure.2: The FTIR spectra of Apixaban and GMS

Differential scanning calorimetry (DSC)

The thermal analysis was estimated by differential scanning calorimetry (Mettler, Star SW 13). The DSC thermogram of Apixaban showed in Figure.3 which showed the sharp peak of onset at 237.03 ^{o}C and decomposes completely at a peak of 239.11 ^{0} C. Furthermore, the Apixaban combined with the GMS was also tested by the DSC showed in Figure.4. The existence of two different peaks in the combined form revealed that Apixaban was found to be compatible with the GMS.

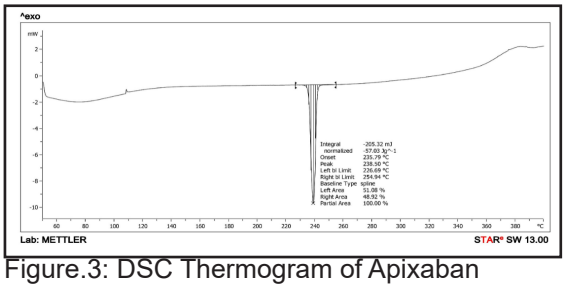

Figure.3: DSC Thermogram of Apixaban

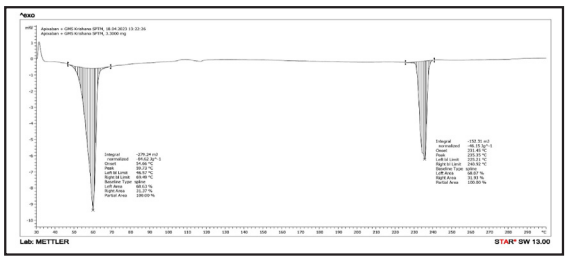

Figure.4: DSC Thermogram of Apixaban and GMS

Box-Behnken design (BBD) for the optimization of SLN

The optimization of SLN comprised a selection of independent factors such as concentration of GMS (X1), PEG 200 (X2), and sonication time (X3). The therapeutic efficacy of the nanoparticles is dependent on the particle size (Y1) and entrapment efficiency (Y2). To perform the optimization analysis, the Design of Expert software (Version 13, Stat-Ease) was applied which suggested Box-the Behnken design model which has less number of trial runs than the central composite design. The BBD showed the 12 runs for the development of the SLN of Apixaban. The batches were coded as S1 to S12 which were in the form of colloidal dispersion. These colloidal solutions were analyzed with the help of Malvern Zetasizer for the analysis of particle size. The BBD was showed in the Table 1. The evaluation of the particle size and entrapment efficiency were placed in the BBD. Further ANOVA was applied which predicted the quadratic model for both the dependent parameters. The p-values for the PS and EE were 0.0332 and 0.0150 respectively. The values found were less than 0.05 hence, the model for the PS and EE was significant. The ANOVA model was depicted in Tables 2 and 3 for the PS and EE respectively.

Table 1: The BBD for the optimization of SLN of Apixaban

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A:GMS	B:PEG 200	C:Sonication Time	Particle Size	Entrapment Efficiency
		mg	ml	Min	nm	%
1	1	40	0.3	25	276	77.87
11	2	45	0.3	30	245	81.95
10	3	45	0.5	20	298	75.67
9	4	45	0.3	20	360	68.69
8	5	50	0.4	30	262.5	79.54
12	6	45	0.5	30	228.5	83.69
7	7	40	0.4	30	250	82.97
4	8	50	0.5	25	262	76.35
2	9	50	0.3	25	325	73.83
5	10	40	0.4	20	309	72.27
3	11	40	0.5	25	260	78.65
6	12	50	0.4	20	320	70.99

ANOVA for quadratic model

Table 2: The ANOVA for the Particle Size

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	16232.94	8	2029.12	9.05	0.0485	significant
A-GMS	693.78	1	693.78	3.09	0.1768	
B-PEG 200	3100.78	1	3100.78	13.83	0.0338	
C-Sonication Time	11325.12	1	11325.12	50.52	0.0057	
AB	552.25	1	552.25	2.46	0.2145	
AC	0.5625	1	0.5625	0.0025	0.9632	
BC	517.56	1	517.56	2.31	0.2260	
A^2	9.03	1	9.03	0.0403	0.8538	
B^2	42.78	1	42.78	0.1908	0.6918	
C^2	0.0000	0				
Residual	672.56	3	224.19			
Cor Total	16905.50	11				

Table 3 The ANOVA Quadratic Model for the Entrapment efficiency

Source	Sum of Squares	df	Mean Square	F-value	p-value	
Model	249.91	8	31.24	20.74	0.0150	significant
A-GMS	15.26	1	15.26	10.13	0.0500	
B-PEG 200	18.06	1	18.06	11.99	0.0406	
C-Sonication Time	205.34	1	205.34	136.31	0.0014	
AB	0.7569	1	0.7569	0.5024	0.5295	
AC	1.16	1	1.16	0.7671	0.4456	
BC	6.86	1	6.86	4.56	0.1225	
A^2	1.36	1	1.36	0.9036	0.4119	
B^2	0.1081	1	0.1081	0.0718	0.8061	
C^2	0.0000	0				
Residual	4.52	3	1.51			
Cor Total	254.42	11				

$PS = +287.50 +9.31 A -19.69 B -37.63 C -11.75 AB +0.3750 AC +11.38 BC -2.13 A^2 -4.62 B^2 +0.0000 C^2$ ..... Equation 1

$EE = +77.27 -1.38 A +1.50 B +5.07 C +0.4350 AB -0.5375 AC -1.31 BC -0.8250 A^2 +0.2325 B^2 +0.0000 C^2$ ..... Equation 2

The ANOVA model predicted the polynomial quadratic equations for both PS and EE which was showed in equation 2 and 3 respectively. The mean particle size and entrapment efficiency for the SLN was 291.35 nm and 77.27 %. The synergistic and antagonistic effects of independent factors on the PS and EE were showed with signs such as plus and minus in equations 1 and 2. In equation 1 for the PS, the synergistic effect was observed with the concentration of GMS and antagonistic effects were indicated by the concentration of surfactant and sonication time. The lipid concentration contributed significantly to achieving the desired particle size and the drug completely dissolved in the lipid matrix.

The combination effects of independent parameters on the dependent factors were reflected by the terms AB, AC and BC respectively in both equations. The lipid and sonication time (AC) as well as surfactant along with sonication time (BC) also showed synergistic effects on the PS. In equation 2 for EE, synergistic effects were indicated by the concentration of surfactant and sonication time. The concentration of GMS has showed antagonistic effects on the EE. The concentration of GMS and surfactant also predicted synergistic action on the EE, while AC and BC indicated antagonistic effects. The entire effects of independent factors on the dependable parameters were showed with the help of 2-D Contour plots and 3-D response surface plots in the Figure 5, 6, 7, and 8 respectively.

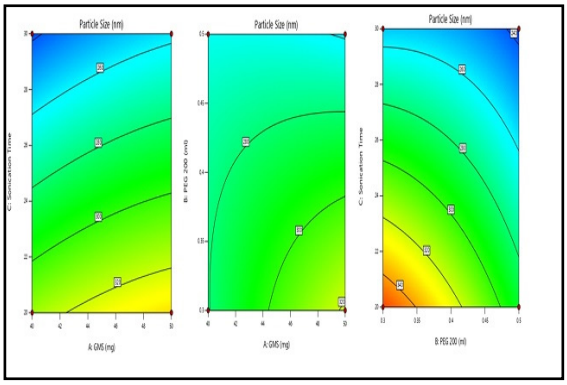

Figure.5: 2-D Contour plot for the particle size

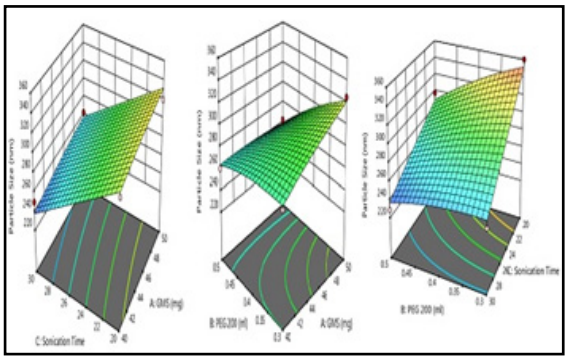

Figure.6: 3-D Response surface plots for the particle size

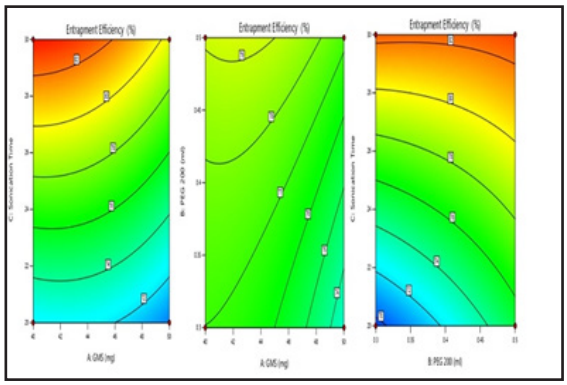

Figure.7: 2-D Contour plot for the entrapment efficiency

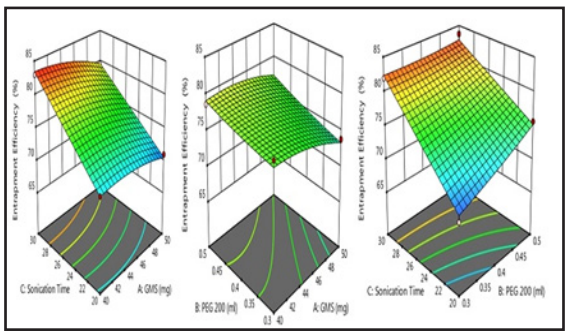

Figure.8: 3-D Response surface plots for the entrapment efficiency

Evaluation of SLN

Determination of PS, PDI, and ZP

The colloidal samples were subjected for their particle size (PS), zeta potential (ZP) and polydispersity index (PDI) by using Malvern Zetasizer. The particle size was observed from 243.9 nm to 360 nm due to the alterations in the concentration of lipid, surfactant and sonication time. The zeta potential was recorded in the range of -15 to -37.4 mV. The PDI was noted from 0.372 to 0.472. Among these 12 prepared batches, F6 was selected as an optimized batch which showed the desired particle size of 243.9 nm, zeta potential of -20.8 mV and PDI value was 0.372 showed in the Figure 9 and 10.

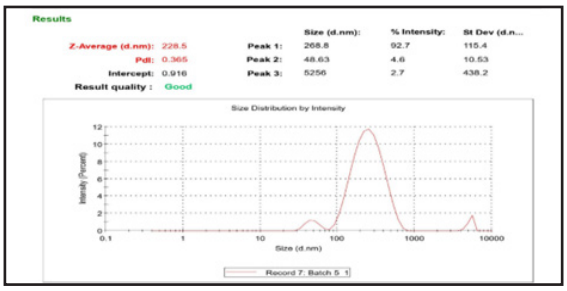

Figure .9: The particle size and PDI of an optimized batch F6

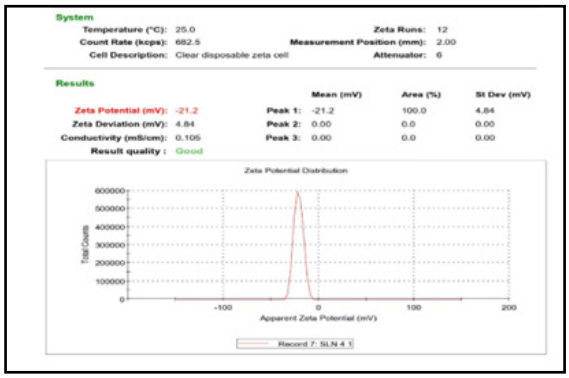

Figure.10: The Zeta Potential of an optimized batch F6

Entrapment efficiency (EE)

The drug entrapment among the several batches was observed in the range of 70.99 % to 83.69 %. The variations in the EE was attributed to the different lipid composition in the batches. The F6 has showed the highest EE, hence selected further for lyophilization.

In-vitro dissolution studies

The in-vitro dissolution study for an optimized batch F6 was carried out in the USP

type I apparatus. The drug release from the SLN showed the biphasic release pattern, initially the speedy release and subsequently the sustained release. The cumulative release of Apixaban from the SLN was 23.83 % within 2 h. The speedy release of Apixaban was credited to the presence of the drug in the outer region of SLN. Afterwards, the release from the SLN was followed the sustained-release pattern for about the next 24 h. The cumulative % of drug dissolved from the optimized Apixaban-loaded SLN was 86.20 %. The sustained action of SLN was due to the higher level of drug entrapped inside the lipid matrix which exhibited slower dissolution. The release mechanism observed was diffusion from the lipid core matrix. The in-vitro release profile of Apixaban -SLN of an optimized batch F6 was showed in Figure. 11.

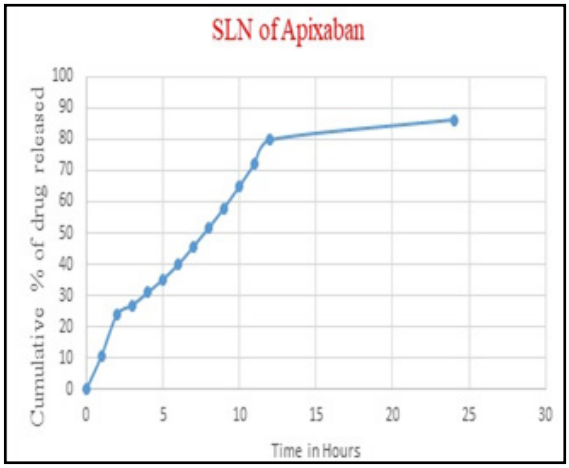

Figure.11: In-vitro drug release profile of F6 SLN of Apixaban

Lyophilization of SLN

The optimized SLN batch F6 was further lyophilized for improved physical and chemical stability. Mannitol was combined as a cryoprotectant and thereby converted colloidal dispersion into the lyophilized powder. The powder obtained was mixed with the excipient and filled into the capsules for oral delivery.

Stability study

Stability was accomplished at the raised temperature and humidity condition to evaluate the quantifiable changes that occurred which affect the physical and chemical stability of the active ingredients. The results indicated that, slight changes observed with PS, and EE but not at a significant level. Hence, the developed SLN batch F6 was found to be stable. The results are depicted in Table 4.

Table 4: Stability assessment of optimized batch F10

Measures	Initial	1 Month	2 Month	3 Month
PS (nm)	243.9	245	250	260
EE %	83.69 ±0.87	83.59±0.98	83.27±0.90	83.05±0.69

Conclusion

There are certain unpredictable conditions arise in the body related to blood clotting such as deep vein thrombosis, and pulmonary embolism, etc. Moreover, many surgical treatments require anticoagulant therapy for a longer period to avoid any further complications. Apixaban is a highly preferred oral anticoagulant over warfarin due to direct its action on the Factor Xa and safety concern point of view. However, the therapeutic efficacy is restricted due to poor bioavailability. Hence, these situations demand modified delivery which provides the sustained action for 24 hours with greater therapeutic efficacy. The Apixaban was loaded in the lipid matrix which enhances the solubility, bioavailability and therapeutic efficacy. Moreover, SLN-Apixaban reduces the frequency of drug administration and thereby improves patient compliance achieved.

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Conflict of interest

None

Declaration: No utilization of any AI tool for writing the manuscript.

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