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Research Article

Development and Optimization of Apixaban-loaded Solid Lipid Nanoparticles by Central Composite Design, *In-vitro* and *Ex-vivo* Characterization

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ABSTRACT

The study's objective is to develop apixaban-loaded solid lipid nanoparticles (SLN), which provide an increased permeability and sustained release compared to tablet formulations. The design of experiments (DoE) is employed in the development and optimization of SLNs. SLNs were manufactured using hot homogenization followed by an ultra-sonication method. Initially, screening of lipids and surfactants (both qualitative and quantitative variability) was done by mixture design. Furthermore, the formulation was optimised using central composite design considering the concentration of both lipid and surfactant as factors and particle size, polydispersity index (PDI), encapsulation efficiency (EE), zeta potential, and percent drug release as responses. Statistical evaluation was performed to get the optimised formulation composition, i.e., glyceryl monooleate (GMO) -6.7% and polysorbate 80-3%. The surface morphology has shown that the SLNs were spherical with a particle size of 239.33 ± 10 nm, PDI of 0.135 ± 0.015, EE of 78.00 ± 2% and zeta potential of -26.4 ± 0.75 mV. %drug release from the optimised formulation was extended to 24 hours. *In-vitro* release showed the initial burst release was followed by a persistent release lasting up to 24 hours. The *ex-vivo* permeation studies revealed that the permeability of the optimised SLN formulation is increased by 1.9 and 1.3 times compared to pure drug and tablet formulations. The stability results showed that the optimised formulations were stable for up to 6 months at 2–8°C and 25 ± 5°C/60 ± 5% RH. These findings suggest that the apixaban SLNs could be used as a delivery system with higher bioavailability and longer drug release.

Introduction

Apixaban, sold under brand name of Eliquis®, which is a factor Xa (FXa) inhibitor, is chemically described as 1-(4 methoxyphenyl) -7-oxo-6-[4-(2-oxopiperidin-1-yl) phenyl] -4,5,6,7-tetrahydro-1H-pyrazolo [3,4 c] pyridine-3-carboxamide. Molecular formula of apixaban is $C_{25}H_{25}N_5O_4$. It's used to prevent systemic embolism and stroke in patients suffering from atrial fibrillation, as well as deep vein thrombosis (DVT) and pulmonary embolism (PE) in patients undergoing hip or knee replacement surgery. The pharmacokinetic data showed that the absolute bioavailability is approximately around 50% of the apixaban dose.[1] According to the clinical pharmacology and biopharmaceutics review, apixaban has high solubility and low permeability (BCS class III molecule).[2,3] As the bioavailability of the eliquis tablets is around 50%, the bioavailability of apixaban can be increased using nanoparticulate drug delivery systems. Solid lipid nanoparticles (SLNs) are a type of nanoparticulate drug delivery system, which are used to improve the drug's solubility and permeability. The main ingredients of SLNs are lipids, which are in a solid-state at normal room temperature conditions, emulsifiers and sometimes combination of both, actives (APIs) and a suitable solvent system.[4] The lipid matrix restricts the mobility of the medicines into the lipid matrix due to the solid structure

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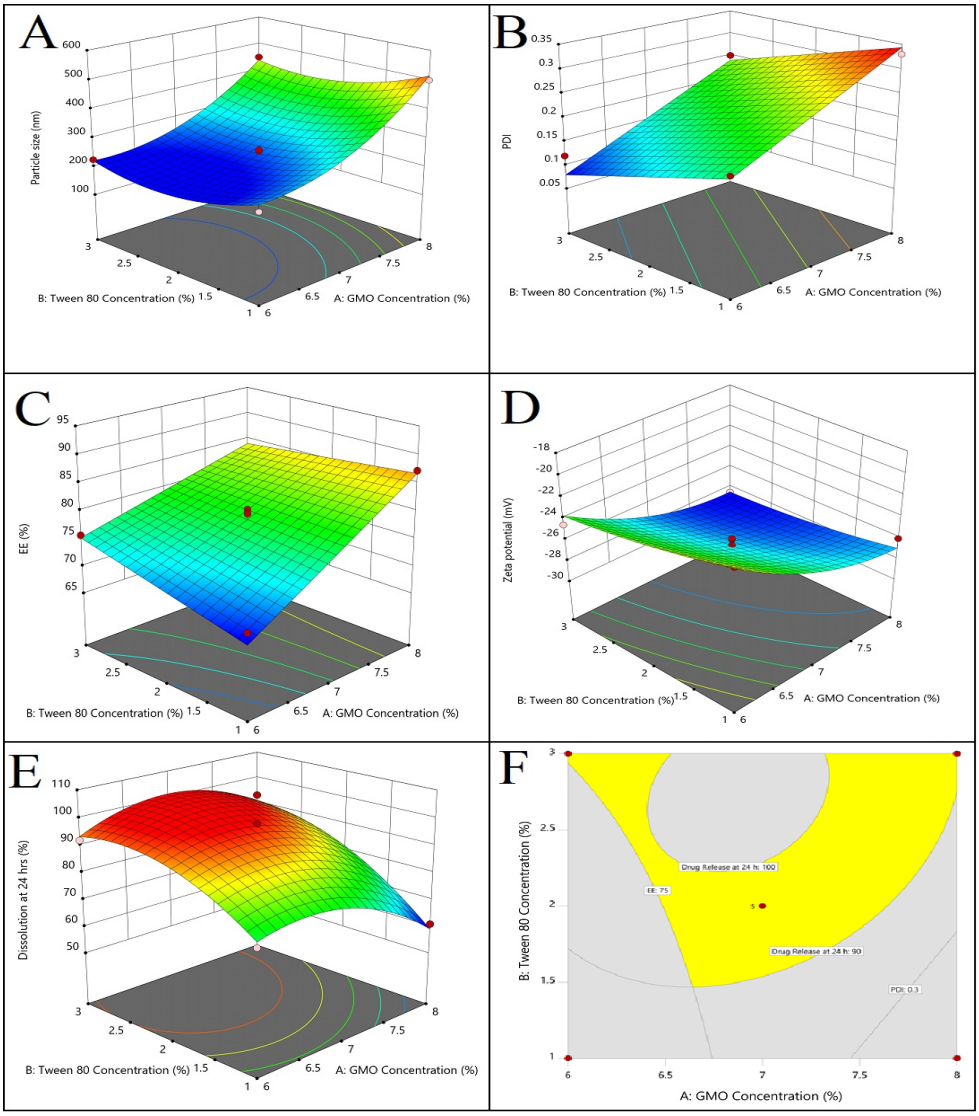

Fig. 1: Response surface plots of: (a) particle size, (b) PDI, (c) encapsulation efficiency, (d) zeta potential (e) drug release at 24 hours and (f) overlay of constraints for optimization of SLNs composition

of the lipids, which is an advantage of the SLN. This also reduces particle coalescence, which enhances stability, limits drug migration into the surfactant film, and leads to long-term drug release. When SLNs are administered orally, they are taken up by the reticuloendothelial system and bypass first-pass metabolism, resulting in improved drug bioavailability. [5]

In this study, an initial screening design was employed to find the suitable lipid and surfactant for the manufacturing of apixaban SLNs. Two lipids glyceryl monostearate (GMS) and glyceryl monooleate(GMO) and two surfactants polysorbate 80 (Tween 80) and span 20 were evaluated for suitability of the formulation. Based on the statistical analysis, GMO and tween 80 were selected for formulation optimization. Central composite design (CCD) is used for the optimization and validation of the optimised formulation. The SLNs generated were stable, spherical in shape, and drug release was sustained for 24 hours, according to the results of the improved formulation.

Materials and Methods

Materials

Apixaban was gifted by Alembic Pharmaceuticals Ltd, India. GMS and GMO was obtained as samples from BASF and Gattefosse SAS, France, respectively. Polysorbate 80 and span 20 were procured from Croda, India. All the other solvents, reagents and chemicals were of analytical grade and procured from Rankem and Merck Chemicals.

Preparation of Apixaban SLNs

Hot homogenization followed by ultra-sonication technique is employed for preparation of SLNs.[6] Drugs and a specified amount of lipid were dissolved in chloroform

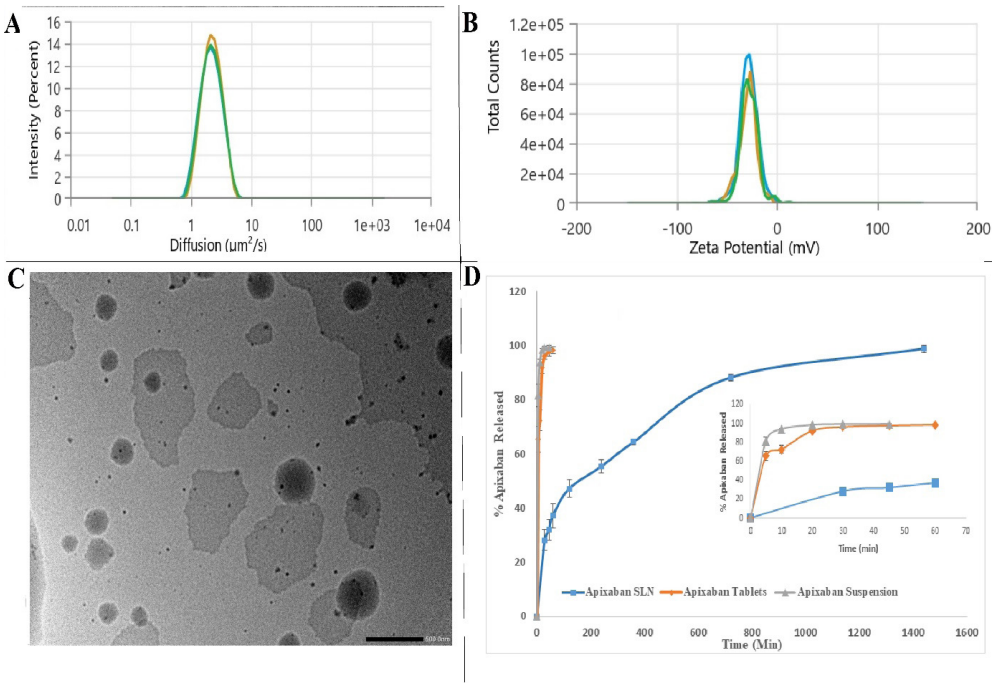

Fig. 2: Characterization of slns. (a) histogram of particle size, (b) histogram of zeta potential, apixaban tablets and apixaban suspension (c) transmission electron microscopic image and (d) *in-vitro* release data of apixaban SLN.

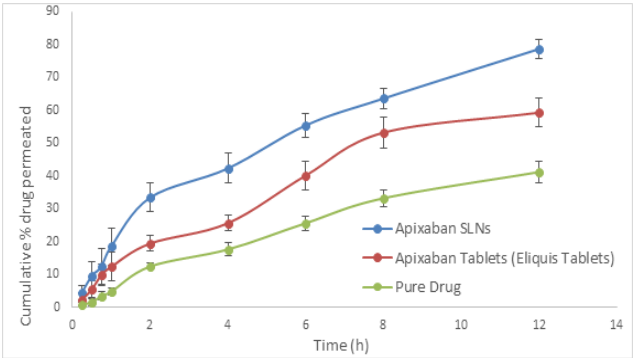

Fig. 3: *Ex-vivo* permeability data of apixaban solid lipid nanoparticles, apixaban tablets (eliquis tablets) and apixaban drug suspension.

and heated to 70°C to form the lipid phase. The surfactant was added to beaker containing hot distilled water (70°C) and stirred to make an aqueous phase. The hot lipid phase was added to the hot aqueous phase and homogenized with the use of a homogenizer (Polytron PT 6100D- Kinematica AG, Switzerland) at 20000 rpm for 15 minutes at 70°C to form oil-in-water emulsion. Then, it was ultrasonicated with an ultrasonicator (Bransonic Ultrasonic bath, Model : CPX8800H-E, Branson Ultrasonics Corporation, USA) for 15 minutes to produce the nanoemulsion. Temperature of the nanoemulsion was rapidly brought down to room temperature and converted into SLNs by immersing the container in an ice bath. The resulting suspension was centrifuged, futher the sediment is redispersed in ultrapure water and lyophilized and kept at 2–8°C until needed.

Experimental Design

In the initial stages, a screening design was used to screen the type of lipid, surfactant, and their concentration in the formulation. After selecting the type of lipid, surfactant, and concentration, a CCD design was used for the formulation optimization.

Screening Design

In this research work, mixture design was employed to screen the variables that affect the formulation of SLNs. In this work, a two-level mixture design with four variables (2 continuous, 2 nominal) was used to screen the main effects of four factors on particle size and encapsulation efficiency (Table 1). Design-expert Software(Stat-Ease, Inc. Version 11.1.2.0). was used for experimental design and statistical analysis.

Optimization Study

After selecting the type of lipid and surfactant, for the optimization of the SLN formulation, a CCD design was used. In this design, lipid concentration and surfactant concentrations are considered 2 variables. These two variables were studied at 5 levels i.e., –α, -1, 0, 1, and + α. The value for α (-1.414) is generated to satisfy the design's orthogonality and rotatability. Table 2 shows the coded and actual values of the variables. A total of 13 runs were performed in accordance with the design matrix created by the design expert (Table 2). Best fit models among the linear, two-factor interaction (2FI) and quadratic models were selected based on the f-value from analysis of variance (ANOVA) results. Equation 1

Table 1: Screening design to evaluate the effect of type of lipid and surfactant and their concentration on particle size and encapsulation efficiency.

	Factors				*Responses**	
Run	*A: Lipid concentration (%)*	*B: Surfactant concentration (%)*	*C: Lipid type*	*D: Surfactant type*	*Particles size (nm)*	*Encapsulation efficiency (%)*
1	6.00	2.00	GMS	Span 20	295.35 ± 2	64.94 ± 1.5
2	4.00	1.58	GMS	Span 20	260.57 ± 4	60.86 ± 0.9
3	4.00	2.00	GMO	Tween 80	223.54 ± 3	71.1 ± 1.2
4	5.42	1.22	GMS	Span 20	270.98 ± 4	64.04 ± 1.0
5	4.72	1.37	GMO	Tween 80	224.57 ± 3	79.94 ± 0.9
6	4.00	1.00	GMO	Span 20	325.14 ± 2	68.65 ± 1.3
7	4.00	1.00	GMS	Tween 80	223.41 ± 5	71.9 ± 0.9
8	6.00	2.00	GMS	Span 20	320.41 ± 4	60.1 ± 1.2
9	6.00	1.00	GMO	Tween 80	235.64 ± 6	79.43 ± 0.7
10	6.00	1.72	GMO	Tween 80	213.98 ± 4	78.4 ± 1.1
11	4.00	1.00	GMS	Tween 80	190.47 ± 2	72.54 ± 0.9
12	6.00	1.00	GMO	Tween 80	238.14 ± 5	76.56 ± 1.3
13	4.00	1.00	GMO	Span 20	323.65 ± 4	69.1 ± 1.1
14	4.00	2.00	GMO	Tween 80	230.54 ± 6	74.4 ± 0.9
15	5.00	1.87	GMS	Tween 80	213.44 ± 3	69.1 ± 0.6

% : Percentage, nm: Nanometer *:Data expressed as mean ± SD (n = 3)

Table 2: Central composite design to evaluate the effect of lipid and surfactant concentrations on repsonses.

		Factors		*Responses**				
Std	*Run*	*A:GMO Concentration (%)*	*B:Tween 80 Concentration (%)*	*Particle size (nm)*	*PDI*	*EE (%)*	*Zeta potential (mV)*	*% Drug release at 24 hours*
1	1	6	1	240 ± 3	0.19 ± 0.023	70.12 ± 0.9	-20.56 ± 1.3	75 ± 1.0
2	2	8	1	500 ± 4	0.33 ± 0.043	87.24 ± 1.2	-26.01 ± 1.0	61 ± 0.8
3	5	6	3	225 ± 2	0.12 ± 0.027	75.68 ± 0.7	-24.51 ± 1.1	92 ± 1.9
4	9	8	3	450 ± 6	0.25 ± 0.032	83.01 ± 0.6	-28.59 ± 0.9	93 ± 1.5
5	8	5.59	2	220 ± 4	0.08 ± 0.042	68.47 ± 1.2	-19.47 ± 1.1	88 ± 0.9
6	6	8.41	2	540 ± 6	0.34 ± 0.053	90.14 ± 1.0	-28.57 ± 01.4	68 ± 1.6
7	13	7	0.59	410 ± 2	0.32 ± 0.043	74.25 ± 0.9	-24.98 ± 1.1	65 ± 1.4
8	12	7	3.41	290 ± 5	0.13 ± 0.044	79.65 ± 1.2	-26.88 ± 0.9	98 ± 1.4
9	4	7	2	235 ± 3	0.19 ± 0.032	80.35 ± 0.3	-26.54 ± 1.5	95 ± 1.0
10	7	7	2	245 ± 5	0.21 ± 0.028	79.58 ± 1.2	-28.01 ± 1.1	98 ± 1.5
11	10	7	2	255 ± 3	0.17 ± 0.036	78.35 ± 0.9	-26.54 ± 0.5	97 ± 1.0
12	11	7	2	236 ± 4	0.21 ± 0.042	77.12 ± 1.1	-25.98 ± 1.3	98 ± 1.0
13	3	7	2	260 ± 2	0.21 ± 0.044	76.98 ± 1.2	-25.88 ± 1.1	98 ± 1.2

%: Percentage, nm: Nanometers, mV: millivolt, *: Data expressed as mean ± SD(n = 3)

shows, how to predict the response using full second-order polynomial equation.

$$Y=\beta_0+\beta_1X_1+\beta_2X_2+\beta_{11}X_1^2+\beta_{22}X_2^2++\beta_{12}X_1X_2 \quad (1)$$

where Y represents expected response(s), β_0 represent intercept, β_1 and β_2 are linear coefficients, β_{11} and β_{22} are squared coefficients, β_{12} represent interaction coefficient, and X_1, and X_2 are independent variables.[7] Design expert software (Stat-Ease, Inc. version 11.1.2.0) was used to conduct statistical analysis.

Polynomial equation's fitness is assessed by verifying the closeness of multiple correlation coefficient R^2

Table 3: Mathematical modeling : Relationship between the variables and responses

Response	*Mathematical equation*
Particle size	246.20+117.9*A-29.34*B-8.75*AB+64.09*A2+49.09*B2
PDI	0.2115+0.0797*A-0.0523*B
Encapsulation efficiency	78.53+6.89*A+1.12*B-2.45*AB
Zeta potential	-26.59-2.80*A-1.15*B+0.3425*AB+1.30*A2+0.3444*B2
%drug release at 24 hours	97.20-5.16*A+11.96*B+3.75*AB-9.47*A2-7.73*B2

A: GMO concentration, B: Tween 80 Concentration

and adjusted R^2(Fit Statistics). The relationship and interaction between the coded variables and responses were demonstrated using three-dimensional surface plots. The optimal points were obtained by solving equations and analyzing the response surface modelling (RSM) plots for the constraints in which particle size (150–350 µ), PDI (less than 0.25), EE (75–100%), zeta potential (-30 to +30 mV) and drug release at 24 hours (90–100%) are controlled at defined levels. To assess the model's precision, optimised formulations were generated in triplicate and the results were compared to the expected values generated by the equation.

High-performance Liquid Chromatography (HPLC) Method

HPLC method was developed based on the method published by Anuja S. Chitale, and Purnima Hamrapurkar.[8] Analysis was done using Inertsil C_{18} -2, 250 x 4.6 mm, 5.0 µ column. The mobile phase was a mixture of 0.01 M sodium acetate buffer (pH 4.5) and acetonitrile at 55:45 ratios. A gradient programme was used to do analyze with 0.8 mL/min flow rate and at 280 nm detector wavelength. The total run time is 15 minutes with a retention time of 6 minutes.

SLNs Characterization

Particle size (z-average diameter), polydispersity index (PDI) and zeta potential were measured by photon correlation spectroscopy using Malvern Zeta sizer nano ZS (Malvern Instruments, UK) at 25°C. Before measuring, the nanoparticles were properly diluted with ultrapurified water. The measurement was carried out at a detection angle of 173°. For each sample, a triplicate analysis was done.

Table 4: Drug release kinetic parameters

	Zero order model	*First order model*	*Higuchi model*	*Korsmeyer-peppas model*
R2	0.9293	0.9699	0.9851	0.9933
k0 (min-1)	0.090	-	-	-
k1 (min-1)	-	0.004	-	-
kp (min-1)	-	-	-	9.770
kh (min-1)	-	-	3.106	-
n	-	-	-	0.323

Encapsulation Efficiency

Before lyophilization, the solid lipid nanoparticle suspension equivalent to 5 mg was added to a test tube. Sample is subjected to centrifugation for 30 minutes at 15000 rpm using an ultracentrifuge. The obtained sediment (pellet) was washed with cold WFI to remove any free drug. This sediment is dissolved in a suitable quantity of methanol to extract the drug from solid lipid nanoparticles. Estimation of the drug content was performed by HPLC using Inertsil C_{18} column at a wavelength of 280 nm.

$$\text{Entrapment Efficiency}(\%) = \frac{\text{Drug present in pellet}}{\text{Theoretical drug quantity present in the SLNs}} \text{X } 100 \quad (2)$$

In-vitro Release Studies

Dialysis bag method was employed for determination of *in-vitro* release. SLNs equivalent to 5 mg of the drug was taken in a dialysis bag (12 kDa molecular weight cut off membrane with a pore size of 2.4 nm). The dialysis bag was dipped in 500 mL of the dissolution medium (0.05 M sodium phosphate buffer containing 0.05% SLS, pH 6.8) to maintain sink conditions[9,10] and kept under continuous stirring at 75 rpm while maintaining the temperature at 37°C. At predefined intervals, a 5 mL aliquot of the release media was removed and replaced with 5 mL of fresh dissolving medium. HPLC was used to determine the amount of released medication in the samples, as discussed in previous sections.

To analyze release kinetics, *in-vitro* release data was fitted into various release order models. For zero-order kinetics, %cumulative amount of drug release was plotted against time whereas first-order release kinetics was studied using log %drug remaining-time plot. Log %cumulative drug release was plotted against log time for Korsmeyer-Peppas model and %cumulative amount of drug release versus square root of time was plotted for the higuchi release model. The correlation coefficient was determined for each model to find out the best-fit release kinetics.[11]

Ex-vivo Permeation Studies[12-14]

Permeability of the BCS Class III drugs was expected to increase in the presence of lipid-based excipients. To simulate the actual permeability of the drug from formulation through the GI membrane, comparative *ex-vivo* permeability studies of apixaban solid lipid nanoparticles, pure drug suspension and marketed formulation (apixaban tablets) were performed using a goat intestinal membrane. Freshly excised fully thick male goat intestinal membranes were collected from a local animal slaughterhouse without causing any damage to the epidermal layer. The collected intestinal membrane was tagged to one end of an open-

ended glass tube and then it was submerged vertically in 50 mL of diffusion medium (0.05 M sodium phosphate buffer with 0.05% SLS, pH 6.8) so that the membrane was immersed 1–2 mm deep into the diffusion medium. Solid lipid nanoparticles, drug suspension and tablets equivalent to 5 mg dose were taken into the donor compartment containing 10 mL of 0.05 M sodium phosphate buffer with 0.05% SLS, pH 6.8. On a magnetic stirrer (Remi, India), the diffusion medium was continuously stirred at 75 rpm while maintaining the temperature at 37 ± 0.5°C.

The HPLC method was employed to quantify the diffused drug content of samples (n=6) taken at predefined time intervals up to 12 hours, sample volume was replaced with fresh buffer after collecting the sample.

Surface Morphology

Transmission electron microscopy(TEM) was used to study the apixaban SLNs surface morphology.[15] Solid lipid nanoparticles were deposited onto carbon-coated grids and images were recorded using Hitachi, H-7500 transmission electron microscope (Hitachi High Technologies, Tokyo, Japan).

Stability Studies

The optimised formulation was tested for stability at two temperatures: 2–8°C and 25 ± 2°C/60 ± 5% RH. Drug content (%), particle size, PDI and zeta potential were estimated every 1, 2, 3 and 6 months.

Result And Discussion

Screening of Effective Factors on Particle Size and Encapsulation Efficiency of SLNs

Mixture design was used to evaluate the two-factor interactions and main effects to determine the variables and interactions that have an influence on particle size and EE of the apixaban SLNs. To screen the effective factors ANOVA followed by an optimization tool was used in Design-expert software. The design matrix, factors and their responses were shown in Table 1. Based on the statistical analysis, all the above models were statistically significant ($p < 0.05$) with an insignificant lack of fit ($p > 0.05$). By using optimization tool, GMO and Tween 80 were selected as lipid and surfactant with quantities of 6 and 1%, respectively.

Central Composite Design for Optimization

From the screening design, GMO and Tween 80 were selected as the lipid and surfactant for the optimization of the formulation at different levels. Lipid concentration and surfactant concentrations were selected as independent variables for formulation optimization. The responses selected for the optimization of the formulations are particle size, PDI, EE, Zeta potential and %drug release at 24 hours.

Design-expert software (version 11.1.2.0, Stat-Ease, Inc.) was used to perform the statistical analysis of the data. According to ANOVA results, a quadratic model, linear model, 2FI models and quadratic model were found to be the best fit, when the particle size (Y1), PDI (Y2), EE (Y3), Zeta potential (Y4), %drug release at 24 hours (Y5) were considered as the responses, respectively. Central composite design runs and their responses were recorded in Table 2.

Statistical analysis (ANOVA) was performed using Design-expert software. All the above models were statistically significant ($p < 0.05$) with an insignificant lack of fit ($p > 0.05$). The mathematical model describing the relationship between variables and responses were shown in Table 3.

The negative coefficients indicate that the independent variable shows the negative effect on the response and the positive coefficient indicates the positive effect on the response. A higher GMO quantity leads to an increase in the viscosity of the formulation, which requires higher energy and stirring times to get the required particle size and PDI. Thus, higher particle size and PDI were observed. Higher GMO quantity ensures the availability of the lipid to entrap the drug, thus higher EE was observed.

An increase in the Tween 80 concentration leads to a decrease in particle size, PDI, zeta potential and an increase in drug release and encapsulation efficiency. This behaviour is attributed to the fact that Tween 80 decreases the surface tension during the homogenization process and during dissolution, which leads to uniform mixing to produce smaller and uniform particles and dissolution of the drug in the dissolution medium, respectively.

The 3D response surface curves were created for each response to evaluate the interaction effects of independent variables. Response surface plots were shown in Fig. 1A to Fig. 1. The response surface plot from the interaction between the GMO concentration (A) and Tween 80 concentration (B) on particle size, PDI, encapsulation efficiency, zeta potential and %drug release at 24 hours was depicted in the Fig. 1A-*f*, respectively.

Optimization of the Formulation

Based on the outcome of the analysis of the results in Design-expert software, an optimization tool was used to finalize the composition of the solid lipid nanoparticles. For optimization, the following constraints were used: GMO concentration is in range (6–8%), Tween 80 concentration is in range (1–3%), particle size to minimize(150–350 nm), polydispersity index to minimize(< 0.25), encapsulation efficiency to maximize (75–100%), Zeta potential is in range (-30 to +30mV) and %drug release at 24 hours to maximize (90–100%) to get the optimized formulation composition i.e., GMO concentration (6.7%) and Tween 80 concentration (3%). At these levels of GMO and Tween 80 concentrations, the predicted responses were as follows:

Table 5: Stability data of Apixaban SLNs.

Time Points	2–8°C				25 ± 2°C/60 ± 5% RH			
	Drug Content (%)	Particle Size (nm)	PDI	Zeta potential (mV)	Drug Content (%)	Particle Size (nm)	PDI	Zeta potential (mV)
Initial	99.5 ± 1.1	242 ± 3	0.14 ± 0.045	-25.6 ± 0.9	99.5 ± 1.1	242 ± 3	0.14 ± 0.045	-25.6 ± 0.9
1 Month	98.5 ± 1.3	235 ± 4	0.16 ± 0.032	-24.6 ± 1.5	98.1 ± 1.5	265 ± 2	0.16 ± 0.032	-23.9 ± 1.2
2 Months	97.6 ± 1.0	250 ± 2	0.13 ± 0.061	-26.5 ± 1.1	97.2 ± 1.0	273 ± 4	0.18 ± 0.054	-24.3 ± 1.4
3 Months	97.4 ± 1.2	240 ± 2	0.15 ± 0.054	-24.7 ± 1.3	96.9 ± 1.3	285 ± 3	0.17 ± 0.035	-23.4 ± 1.1
6 Months	97.0 ± 1.1	243 ± 4	0.14 ± 0.026	-25.3 ± 1.2	96.5 ± 1.1	280 ± 2	0.16+0.034	-25.2 ± 1.4

*: Data expressed as mean ± SD(n = 3)

-particle size: 239.33 nm; PDI: 0.14; EE: 78.33%, Zeta potential: -26.54 mV and dissolution at 24 hours: 101.01%.

Experimental Validation

Three experiments were performed with optimized composition and results were compared with predicted values. The responses were particle size of 235.2 ± 10 nm (Fig. 2A), polydispersity index of <0.2, encapsulation efficiency of 78 ± 2%, zeta potential of -26.54 ± 1 mV (Fig. 2B); dissolution at 6 hours of 66 ± 2%, dissolution at 12 hours of 87.5 ± 1.5% and dissolution at 24 hours of 98.5 ± 1.5%. The observed and predicted values are within the 95% confidence interval confirming the validity and precision of the model.

Surface Morphology

TEM reveals that the solid lipid nanoparticles were formed spherical in shape and size is well below 350 nm. The TEM images (Fig. 2C) also revealed that formed particles are uniform in size.

In-vitro Release Studies

In-vitro release studies of the optimized formulation, were performed along with drug suspension and tablets formulation (Fig. 2D). Complete drug release was observed in 45, 60 and 1440 minutes for apixaban suspension, apixaban tablets and apixaban SLNs, respectively. A biphasic release pattern was observed for solid lipid nanoparticles. The initial rapid release of the drug is due to the weekly bounded drug on the surface of the solid lipid nanoparticles. Around 48% of the drug is released within 2 hours of the dissolution. Drug release data is fitted into various mathematical models. Based on the release rate constants and correlation coefficient of various models (Table 4), showed that the drug release followed the power law (Korsmeyer-Peppas equation). Based on the n-value of 0.323 calculated from the Korsmeyer-Peppas equation, the drug release was found to be fickian diffusion.

Ex-vivo Permeation Studies

Ex-vivo permeation was conducted on apixaban solid lipid nanoparticles, pure drug and tablets. Comparative results of permeability studies are represented pictorially in Fig. 3. From the Fig. 3, it can be understood that the solid lipid nanoparticles shown better permeability than the tablets (1.3 times higher) and pure drug (1.9 times higher). More than 79.0+2.9% of the drug was diffused within 12 hours from solid lipid nanoparticles, whereas 59.0 ± 4.3% and only 41.0 ± 3.3% of apixaban was diffused from tablets and drug suspension, respectively.

Stability Studies

Stability studies results (Table 5) showed that Apixaban solid lipid nanoparticles were found to be more stable at 2–8°C compared to 25 ± 2°C/60 ± 5% RH stability condition. Drug content is decreased by less than 5% after 6 months of storage in the 25 ± 2°C/60 ± 5% RH stability condition, this might be due to the change in the solidification behaviour of lipids at 25°C compared to the 2–8°C. The other parameters were well within acceptable limits.

Conclusion

Apixaban solid lipid nanoparticles prepared by hot homogenization by ultra-sonication method by employing design of experiment studies. Optimized formulation showed sustained release compared to the tablet formulation. Sustained release of apixaban can be utilized to reduce the dose to be administered or decreasing the dosage regimen of the apixaban formulations can be achieved.

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CONFLICT OF INTEREST

None.

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None.

ETHICS STATEMENT

None.

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