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Original Article

Development Optimization, and Characterization of Solid Lipid Nanoparticles of Entacapone for Treatment of Parkinson Disease

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ABSTRACT

Introduction: Entacapone is recommended for treating Parkinson's disease. **Objectives:** Entacapone's high lipophilicity showed limited therapeutic efficacy in therapeutic doses. Moreover, the short half-life enabled frequent dosing, which resulted in high toxicity. Hence, the current research aimed to improve the solubility of Entacapone and thereby accelerate the absorption and efficacy via Solid Lipid Nanoparticles (SLN). **Materials and Methods:** FTIR assessed the drug identification and compatibility. The DSC and XRD estimation confirmed the thermal nature and crystalline characteristics of the Entacapone. The solubility estimation was performed on several solid lipids and surfactants. SLN was developed using high-speed homogenization and probe sonication methods. **Results:** Glyceryl monostearate and Tween 20 were identified to be the best lipid and surfactant. The Box-Behnken design model was opted for the optimization of SLN, and further ANOVA was applied. The extent of lipid, surfactant, and sonication time was an independent variable. The particle size and entrapment efficiency were critical quality attributes for developing SLN. The best particle size achieved was 143.1 nm and -13 mV *Zeta Potential* with F9. The preferred batch F9 showed an entrapment efficiency of 88.67%. The *in vitro* release from SLN showed rapid release of the drug for an initial 2 hr. and later sustained release for about 24 hr. The optimized batch showed marked stability when assessed at 40ºC and 75 % RH for 3 months. **Conclusion:** The enormous improvement in solubility was attained via SLN, and the sustained released profile also boosted patient comfort and compliance.

Keywords: Entacapone, Solid lipid nanoparticles, Box-Behnken design, Parkinson's disease.

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INTRODUCTION

One of the best lipid-based nanoparticles is Solid Lipid Nanoparticles (SLN). This system consists of lipids in the form of solids and behaves as a colloidal dispersion. The stabilizer in the form of a surfactant is an essential component of SLN.[1] The popularity of SLN is rising continuously for enhancing the solubility and bioavailability of hydrophobic molecules due to their biocompatible and biodegradable nature.[2] The several dosage forms, oral, parenteral, ocular, rectal, and topical, are prepared via SLN, which makes them unique.[3] Moreover, SLN-mediated drug delivery enabled the release of medicament sustainably, providing patients comfort and high compliance.[4]

Thus, dosing frequently is minimized, and hence, adverse effects are circumvented by SLN-loaded actives.[5] Another interesting feature of SLN is the protection of actives from external environmental factors such as temperature, light, and humidity.[6] The laboratory preparations and commercial manufacturing of SLN are similar and simple compared with other nanoparticle production methods. Several researchers utilize SLN as a first choice because of its safety due to the lack of organic solvent utilization.[7] The numerous methods employed for the preparations are hot homogenization, cold homogenization, and melt emulsification.[8]

Parkinson's Disease (PD) is the second most fatal neurodegenerative disorder affecting more than 30 million people globally.[9] This disease occurs due to a deficiency of dopaminergic neurons in the brain. It is identified by tremors and bradykinesia.[10] Moreover, the dysfunction of mitochondria, oxidative stress, mitochondrial DNA mutation, excessive reactive oxygen species generation, and aggregation of proteins lead to the development of PD. The diagnosis of PD is most challenging and occurs due to

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genetic and environmental factors. The proper medication helps in minimizing the symptoms associated with PD.[11,12]

Entacapone is most widely utilized for the treatment of Parkinson's disease.[13] It works by suppressing the action of *catechol-O-methyl transferase*.[14] Entacapone is absorbed in the body by the oral route. The log *p*-value of entacapone is 2.8, and the reported water solubility is 0.0797 mg/mL. The bioavailability of entacapone is only 35%, and the half-life is 0.4-0.7 hr.[15]

The current industrial practice for manufacturing is implementing the Quality by Design approach. The best part of QbD is the systematic development of dosage forms with prior knowledge of risk factors and errors.[16] Moreover, minimal trials save time and material, an utmost requirement in the pharmaceutical industry. The prime element of QbD is critical quality attributes, which are mainly related to the patient's efficacy and therapeutic action.

MATERIALS AND METHODS

Entacapone was gifted by Intas Pharmaceutical, Ahmedabad. Solid lipids were supplied by Ajanta Pharmaceutical, Aurangabad. Surfactant was purchased from Loba Chemicals, Mumbai. All the chemicals and solvents utilized for estimation were of analytical grade only.

Selection of lipid

The estimation of solubility in the lipid is the utmost criterion for the successful development of SLN. The several solid lipids were weighed and transferred into the test tubes. These test tubes were placed in the water bath to melt the solid lipids above 5-10°C of their melting point. The definite extent of entacapone was added to the molten lipid. Further, test tubes were placed on the vortex mixer and observed for transparency. Furthermore, the content was analyzed spectrophotometrically by UV at 378 nm.[17,18]

Selection of surfactant

The appropriate surfactant minimizes the interfacial tension between both phases. Hence, the selection of surfactant is also vital for the development of SLN. Several surfactant was transferred into the test tubes, and a drug was added. Further, these test tubes were stirred on a vortex mixer and analyzed by a UV-visible spectrophotometer.[19,20]

FTIR

The compatibility between the drug and excipients is very crucial for better therapeutic efficacy. The Solid sample of the drug was analyzed for the recognition of originality. Further, the drug sample was mixed with lipids and surfactants to check for any kind of interaction among them. The scanning range was 400 to 4000 cm.[21]

Differential Scanning Calorimetry (DSC)

Differential scanning calorimetry is capable of estimating the thermal behavior of compounds. Initially, the active ingredient was kept under inert nitrogen at a temperature of 50°C to 400°C.[22,23]

XRD

XRD assessed the internal arrangements and crystalline nature of the active ingredient. The method was determined to scan at 2 Θ in the range of 5-900 and provide a current of 45 kV and 40mA, respectively.[24]

Optimization of SLN

For the optimization of SLN, the concentration of lipid (X1), surfactant (X2), and high-speed homogenization speed (X3) were considered independent variables. The beneficial activities from the SLN are obtained from particle size (Y1) and entrapment efficiency (Y2). The PS and EE are CQAs for the preparation of the SLN. There are 3 independent and 2 dependent factors involved, hence, the Box-Behnken design model was applied. Thereafter, ANOVA was also implemented to analyze the influence of independent variables on the PS and EE.[25-27]

Formulation of SLN

The SLN of Entacapone was prepared by the process of Hot homogenization and the probe sonication method. The optimized extent of GMS was weighed accurately and transferred into the small beaker, which was further kept in a hot water bath. The GMS was heated until it melted entirely above 10°C above its melting point. Milli Q water was heated at the same temperature as GMS in another beaker. Further, this lipid phase was kept under constant stirring, and gradually aqueous phase was added to build oil in an oil-in-water emulsion. This emulsion was kept under a high-speed homogenizer at a speed of 15000 rpm, followed by probe sonication. This resulted in the development of ultra-file globules in nanosized. The obtained dispersion was cooled and stored in the refrigerator at 4°C for further estimation.[28,29]

Evaluation of the SLN of Entacapone

Estimation of PS and ZP

The developed SLN samples of every batch were analyzed for their PS and ZP using Malvern Zetasizer based on dynamic light scattering principles.[30,31]

Estimation of EE

The entrapment of actives was assessed by centrifuging the colloidal dispersion at 16000 rpm to detach unentrapped molecules. Thereafter, the solution was analyzed spectrophotometrically by UV scanning at 378 nm.[32] The content of EE was calculated by using the following equation:[33,34]

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

In vitro release of drug

The dialysis bag method was preferred for the estimation of Entacapone-loaded SLN. The apparatus was operated by revolving at 50 rpm with 0.1 N HCl for initially 2 hr, and later replaced with 5.5 pH phosphate buffer. The samples were withdrawn at intervals of 1, 2, and up to 24 hr and replaced immediately with the phosphate buffer. The samples were analyzed by UV scanning at 378 nm in triplicate.[35,36]

Lyophilization

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°C and further lyophilized at -52°C at a pressure of 0.002 mbar for 48 hr to get a lyophilized powder sample. The obtained sample was filled into the capsule for oral delivery.[37,38]

Accelerated stability assessment

The preferred batch samples were properly packed and kept in the Remi stability chamber at 40°C and 75% RH. These samples were withdrawn for 30 days and analyzed further for their PS and EE.[39,40]

RESULTS AND DISCUSSION

Selection of lipid

The lipid that assimilates a greater extent of the active ingredient was chosen to develop SLN. According to the solubility analysis, the highest extent of entacapone was dissolved in the Glyceryl monostearate (54 µg/mL). The solubility of Entacapone was slightly lower in glyceryl behenate (49 µg/mL) and glyceryl distearate (44 µg/mL). Therefore, GMS was opted for the development of SLN.

Selection of surfactant

The surfactant plays a pivotal role in the development of SLN by reducing the interfacial tension between the solid and liquid phases. Moreover, they also worked as stabilizers for the colloidal dispersion. Hence, the selection of the most suitable surfactant is essential during SLN delivery. Among several surfactants, the greatest solubility of Entacapone was observed in Tween 20 (59 µg/mL), Tween 80 (57 µg/mL), PEG (40 µg/mL), and Span 80 (34 µg/mL). Thus, Tween 20 was preferred over other surfactants in developing the SLN.

FTIR

The FTIR sharp peaks recognized the Entacapone's originality. From Figure 1, a sharp, intense peak at 1620.13 cm^{-1} was identified for the existence of carbonyl stretching in the amide group. Another peek at 1565.83 cm^{-1} was attributed to NO2 stretching, 1439.34 cm^{-1} for O-H bending, 1322.41 cm^{-1} for CH3 bend, 1295.84 cm^{-1} and 1285.07 cm^{-1} contributed to C=N stretching vibrations. The linking of Entacapone with its formulation ingredients retains the peaks, and thus, no therapeutic benefit of Entacapone was lost. The FTIR spectra are shown in Figure 1.

DSC

DSC examined the active compound's thermal behavior, which showed a sharp endothermic peak at 165.59°C and melted entirely at 175.61°C. The physical mixture of Entacapone and lipid melted at 64.56°C in their 1:4 proportion. This indicated

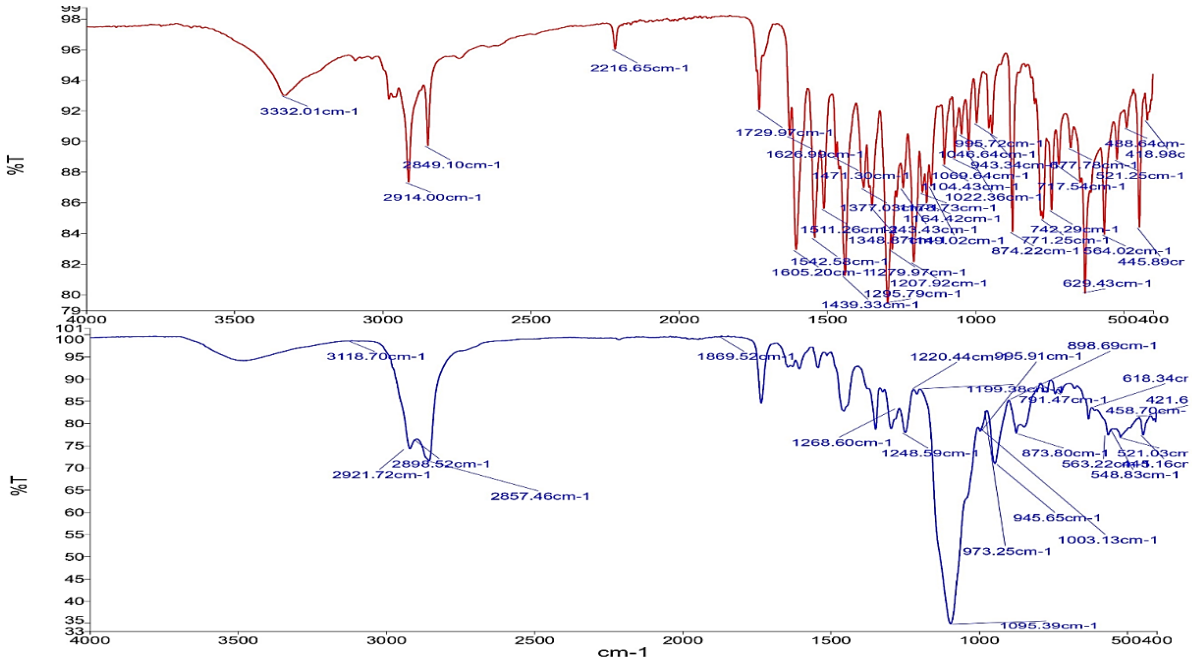


Figure 1: FTIR spectra of Entacapone and GMS.

that Entacapone was dissolved in the melted lipid matrix and hence its peak disappeared at 165°C. Furthermore, the existence of Entacapone in the form of SLN indicated an amorphous nature and uniformity among the samples. The DSC thermogram is displayed in Figure 2.

XRD

The X-ray diffraction helps in understanding the crystalline nature of the medicinal compound. The crystalline nature was predicted by 2 Θ values observed at 9.315°,12.127°, 13.882°, 14.406°, 19.037°, 22.200°, 23.660°, 27.128°, 29.341°, and 30.390°. The amalgamation of Entacapone and GMS significantly reduces the intensity of peaks and is observed at 8.872°, 13.397°, 18.929°, 23.066°, and 26.590°. Therefore, it was interpreted that the crystalline nature of Entacapone was reduced and transformed into an amorphous state. The XRD plots are displayed in Figure 3.

Optimization of SLN

For the optimization analysis, the Design of Expert software (StatEase, Version 13) was applied. With predetermined 3-formulation parameters, their impact on the PS and EE was assessed. Accordingly, the Box-Behnken design model was opted for compared with the central composite design for offering less number of trials. Hence, material and time are both spared by using the BBD. The model depicted a total of 12 trials, which were developed by high-speed homogenization and probe sonication methods. The individual batches were analyzed, and the results were depicted in Table 1. Furthermore, the outcomes of PS and EE were subjected to ANOVA, and the model was found significant with *p*-values of 0.0337 and 0.0299, correspondingly showed in Tables 2 and 3.

The ANOVA for both dependent parameters was elaborated by the polynomial quadratic equations.

$$\text{Particle Size: } +239.25 +28.37\,A+3.00\,B -46.38\,C -17.50\,AB+8.25\,AC+1.0000\,BC -8.00\,A^2-29.25\,B^2 +0.0000\,C^2 \quad \text{Equation 1}$$

The + and - signs indicate that the factors have synergistic and antagonistic effects. The keywords A, B, and C signify the concentration of lipid, surfactant, and sonication time. Moreover, the combined term illustrates the linking effects of independent factors on the PS and EE. The mean PS from the entire batch was 239.2mm, and it complies with the SLN. Most of the successful SLN lies between 100 to 250 nm. The extent of lipid and surfactant displayed a synergistic impact, while the PS and sonication time had a negative impact.

The amalgamation of lipid and surfactant with sonication time showed a synergistic effect. The combination of lipid and surfactant showed here negative impact. In real practice, an appropriate amount of surfactant is essential for minimizing interfacial tension between solid and lipid phases and is also necessary for the stabilization of the colloidal dispersion.

$$EE=+85.33-2.01\,A+0.03281\,B+1.90\,C +0.7425\,AB -0.6100\,AC-0.9787\,BC-1.21\,A^2-0.3134\,B^2 -0.5709\,C^2 \quad \text{Equation 2}$$

The mean EE of SLN was 85.33% and which indicates a high extent of actives are loaded inside the lipid matrix. The extent of

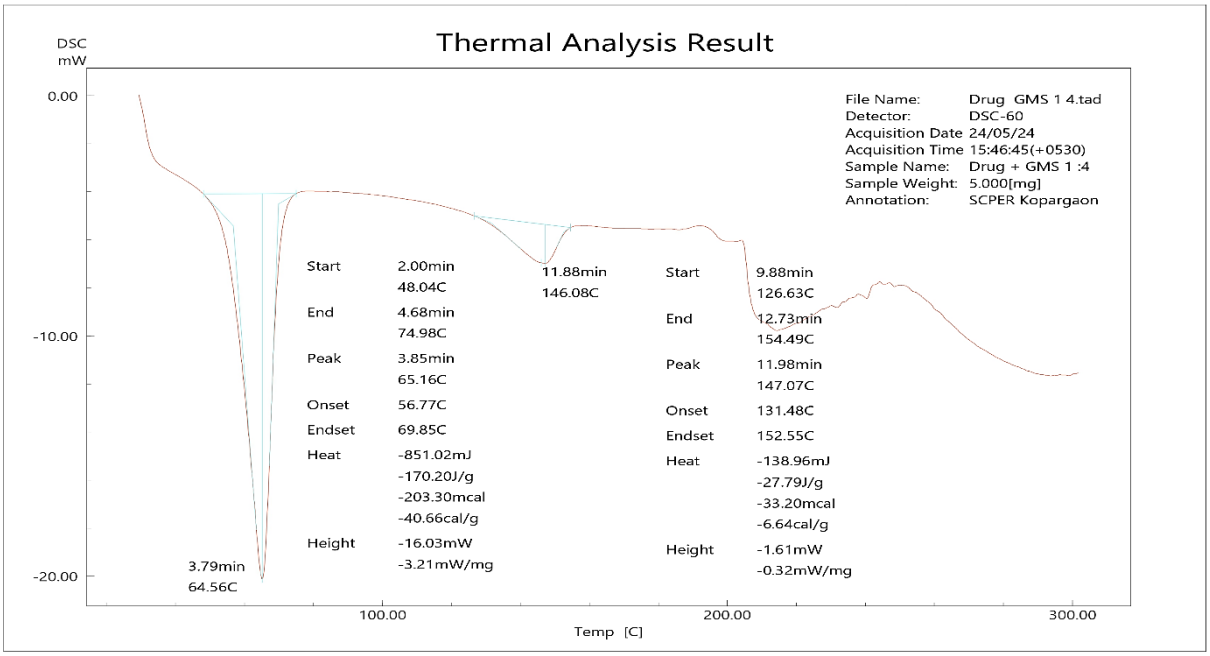


Figure 2: DSC thermogram of Entacapone and GMS.

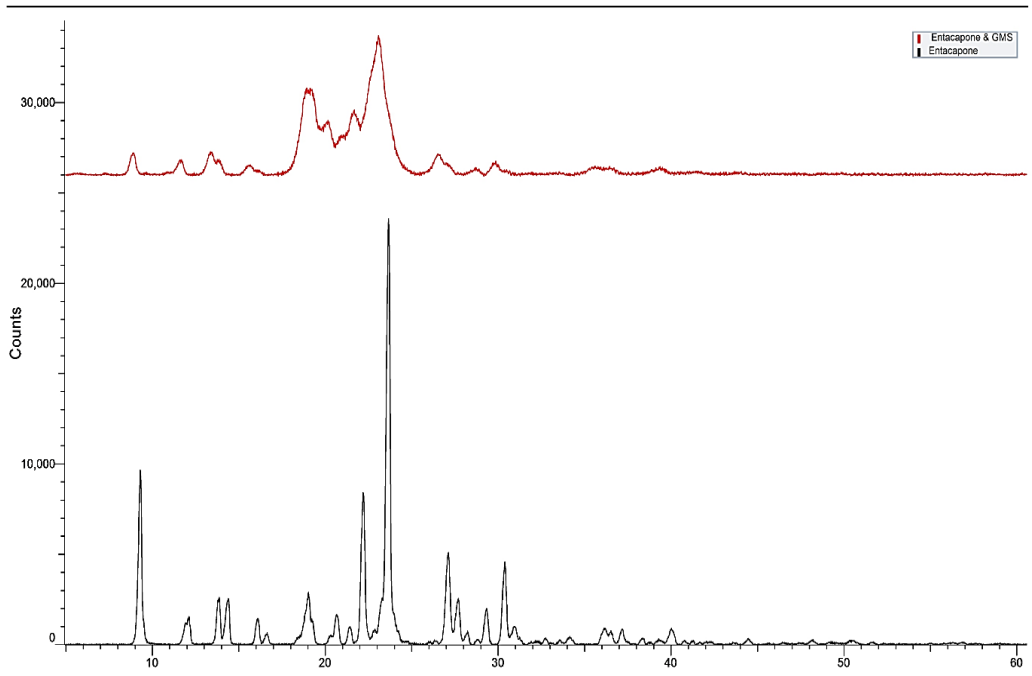


Figure 3: XRD overlay plot of Entacapone and GMS.

Table 1: Box-Behnken Design for SLN.

		Factor 1	Factor 2	Factor 3	Response 1	Response 2
Std	Run	A: GMS	B: Tween 20	C: Sonication Time	Particle Size	Entrapment Efficiency
		mg	%	min	nm	%
3	1	325	1	10	249	81.23
8	2	350	1.5	15	209	83.12
5	3	350	1.25	10	303	80.01
12	4	350	1	15	245	80.99
11	5	300	1	15	160	85.98
9	6	325	1	20	158	86.99
6	7	300	1.5	15	194	85.14
2	8	350	1.25	20	223	82.57
10	9	300	1.25	20	143	88.31
4	10	300	1.25	10	256	83.31
1	11	325	2.5	10	260	81.56
7	12	325	1.5	20	173	85.7

surfactant and sonication time showed synergistic action, and lipid content showed antagonistic action. The amalgamation of lipid and surfactant indicated a synergistic effect. During the estimation of EE, it was observed that the particle size of the colloidal dispersion played a crucial role in it. The smaller particle size has the maximum entrapped drug compared with a bigger one. The impact of both PS and EE was displayed in 2-D Contour and 3-D response surface plots in Figures 4 to 5, respectively.

Determination of PS and ZP

The PS and ZP of all batches were estimated by the Malvern Zetasizer. The PS was observed in the range of 143 nm to 303 nm. Similarly, ZP varied from -7 mV to -24 mV. The preferred PS and ZP of the batch F9 were 143.6 nm and -19.1 mV. The variations in the PS and EE were attributed to the variable extent of lipid, surfactant concentration, and sonication time. A sufficient amount of surfactant is needed for the stabilization of the colloidal dispersion and also for the minimization of interfacial tension. When the surfactant concentration was less or more, it resulted

Table 2: ANOVA for Quadratic Model containing Particle Size.

Source	Sum of Squares	d_f	Mean Square	F-value	*p*-value	
Model	27058.23	9	3006.47	29.09	0.0337	significant
A-GMS	6441.13	1	6441.13	62.33	0.0157	
B-Tween 20	25.52	1	25.52	0.2470	0.6685	
C-Sonication Time	11071.69	1	11071.69	107.13	0.0092	
AB	1225.00	1	1225.00	11.85	0.0750	
AC	272.25	1	272.25	2.63	0.2460	
BC	13.78	1	13.78	0.1334	0.7500	
A^2	532.64	1	532.64	5.15	0.1512	
B^2	2.20	1	2.20	0.0212	0.8975	
C^2	1581.36	1	1581.36	15.30	0.0596	
Residual	206.69	2	103.34			
Cor Total	27264.92	11				

Table 3: ANOVA for Quadratic Model containing Entrapment Efficiency.

Source	Sum of Squares	d_f	Mean Square	F-value	*p*-value	
Model	76.22	9	8.47	32.85	0.0299	significant
A-GMS	32.20	1	32.20	124.90	0.0079	
B-Tween 20	0.5742	1	0.5742	2.23	0.2741	
C-Sonication Time	19.16	1	19.16	74.34	0.0132	
AB	2.21	1	2.21	8.55	0.0997	
AC	1.49	1	1.49	5.77	0.1382	
BC	1.92	1	1.92	7.43	0.1123	
A^2	1.44	1	1.44	5.58	0.1419	
B^2	1.83	1	1.83	7.08	0.1170	
C^2	0.5886	1	0.5886	2.28	0.2699	
Residual	0.5156	2	0.2578			
Cor Total	76.73	11				

Table 4: Stability valuation of optimized batch F9.

Parameters	Initial	30 Days	60 Days	90 Days
PS	143.6 nm	149 nm	158 nm	167 nm
ZP	-19.1 mV	18.9 mV	17.3 mV	15 mV
EE	88.31	87.93	87.14	86.50

in a greater particle size. The desired PS and ZP of an optimized batch F9 were shown in Figure 6.

Estimation of EE

The greater EE of the active ingredient is useful for availing the therapeutic benefits from its dosage form. The maximum EE achieved in batch F9 was 88.31%. The extent of lipids played a significant role in EE. The EE among the batches varied from 80.01 to 88.31%.

In vitro release of SLN

The release profile of actives from SLN was determined using the USP type 1 apparatus. The released profile of SLN showed a dual-released pattern. In the initial 2 hr, faster release of the active was noted from the SLN-loaded Entacapone. The rapid release was attributed to the availability of Entacapone on the outer surface of the lipid matrix. The cumulative release of 18.44% was noted within the initial 2 hr. This prompt release helps in the rapid absorption, thereby providing prompt relief in patients suffering from PD. Moreover, SLN-mediated Entacapone is also favorable

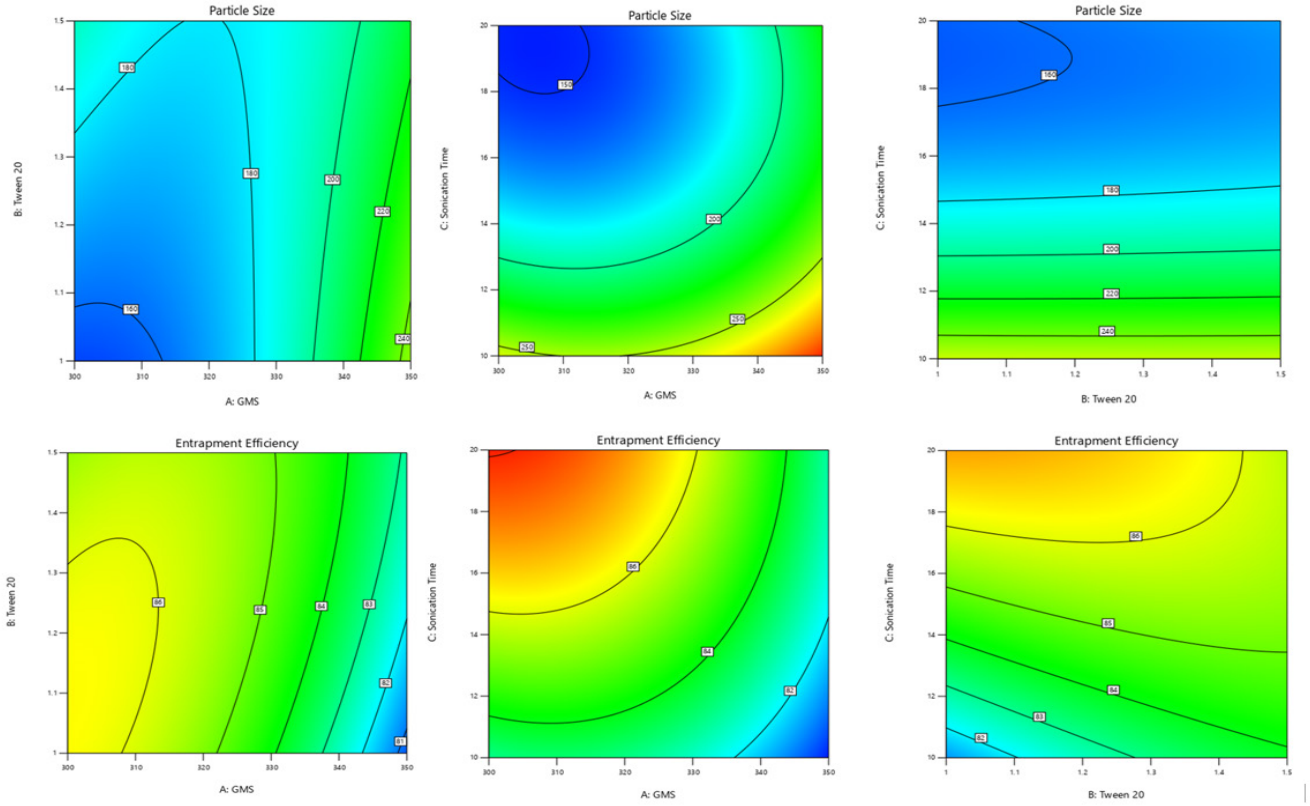


Figure 4: 2-D Contour plots indicate the effects of independent factors on the PS and EE.

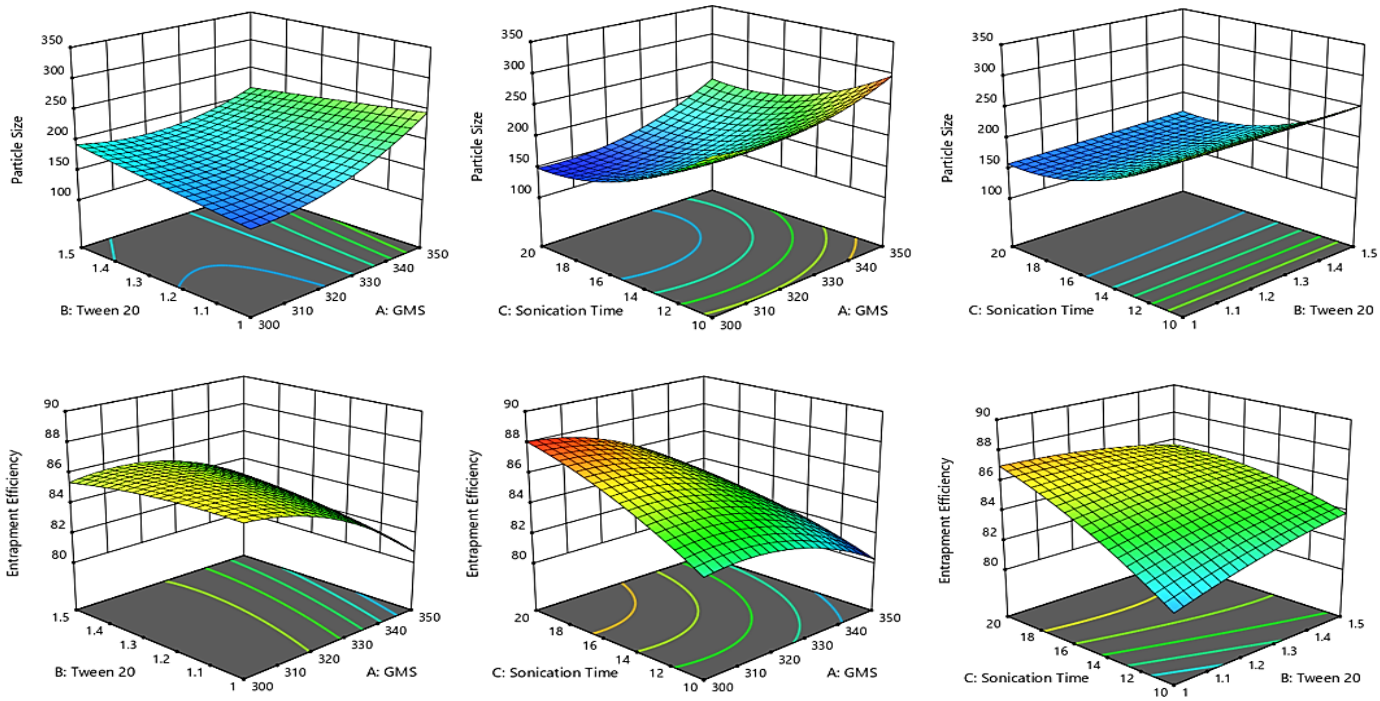


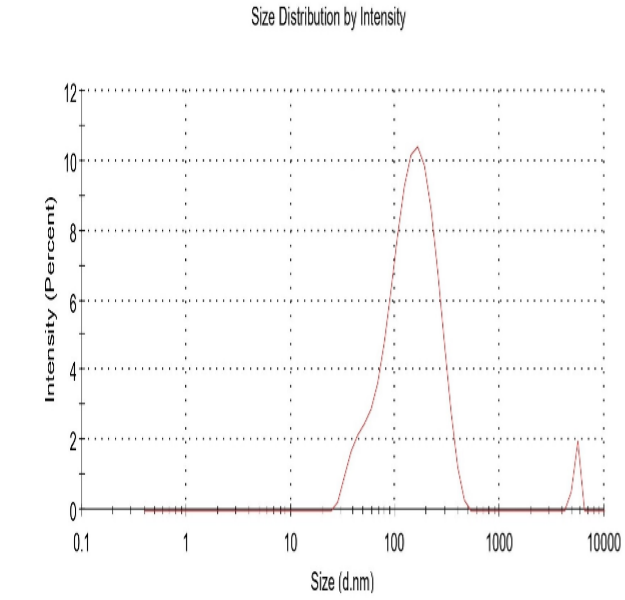
Figure 5: 3-D plots indicated the effects of independent factors on PS and EE.

		Size (d.nm):	% Intensity:	St Dev (d.n...
Z-Average (d.nm): 143.6	Peak 1:	157.5	97.5	81.45
PdI: 0.430	Peak 2:	5395	2.5	312.9
Intercept: 0.960	Peak 3:	0.000	0.0	0.000

Result quality : Good

		Mean (mV)	Area (%)	St Dev (mV)
Zeta Potential (mV): -19.1	Peak 1:	-19.1	100.0	4.99
Zeta Deviation (mV): 4.99	Peak 2:	0.00	0.0	0.00
Conductivity (mS/cm): 0.147	Peak 3:	0.00	0.0	0.00

Result quality : Good



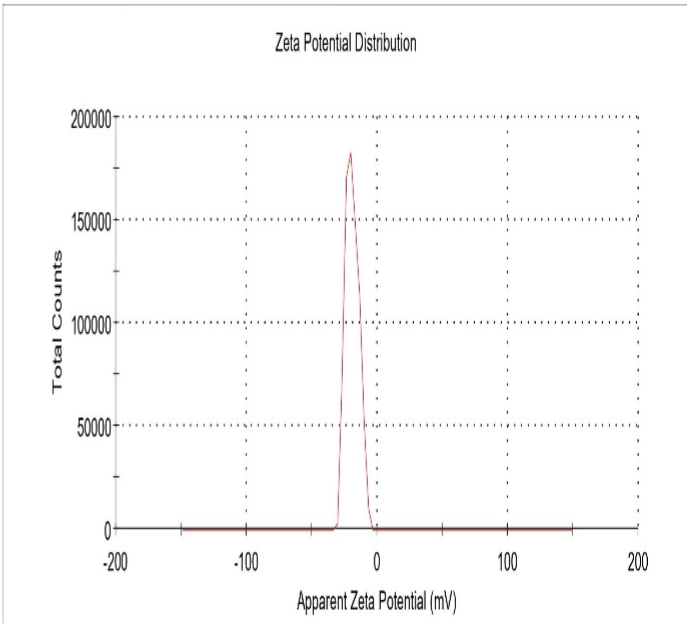


Figure 6: Particle size of an optimized batch F9.

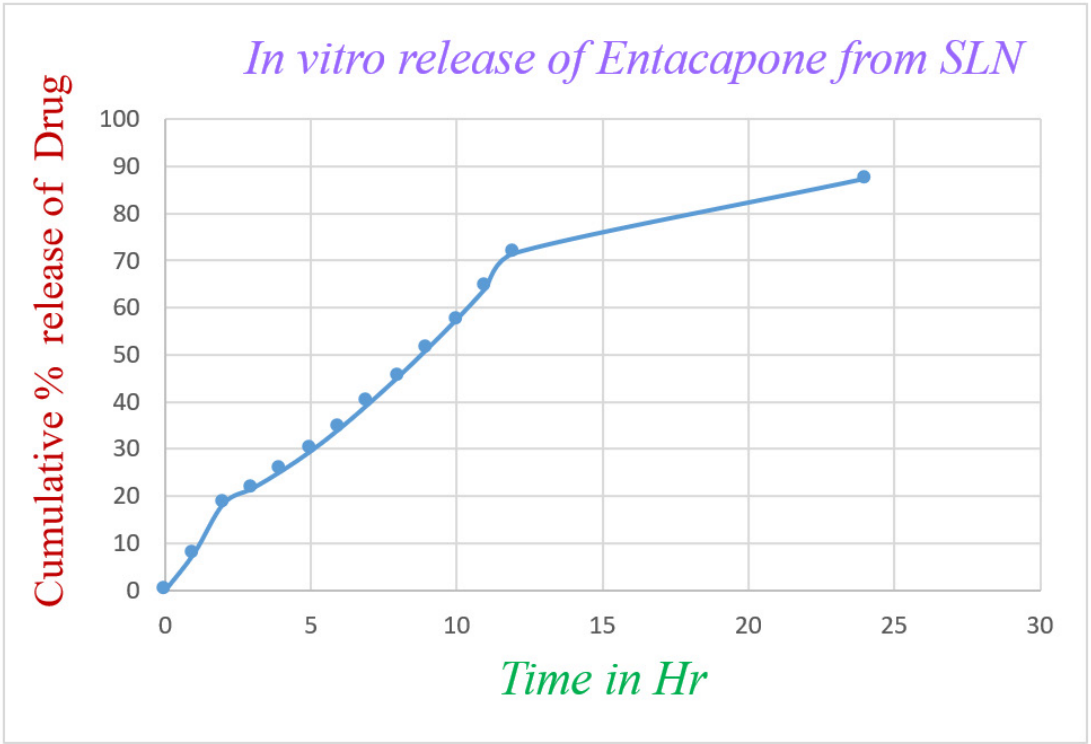


Figure 7: *In vitro* release of Entacapone.

for its sustained release action, which minimizes the repetitive dosing frequency and higher toxicity.

The release of the medicament after 2 hr was very slow due to the non-existence of the drug in the outer lipid layer. The steady release was the inner lipid matrix; hence, sustained delivery is feasible to combat symptoms associated with PD. The cumulative release of 71.67% and 87.44% was observed after 12 and 24 hr. The released profile of an optimized batch F9 was showed in Figure 7.

Stability studies

The preferred batch F9 was assessed under standard stability conditions at 40ºC and 75%. The outcome of the result indicated that SLN-loaded Entacapone showed superior stability. The results are depicted in Table 4.

CONCLUSION

Parkinson's disease is one of the major neurodegenerative diseases that affects the entire body. The progressive disease conditions worsen life and become fatal. Hence, such a disease requires prompt treatment with continuous medication. Entacapone is effective in the treatment of PD, but its poor solubility, lower efficacy, and short half-life are troublesome. The SLN-loaded Entacapone not only enhances the solubility, bioavailability, and therapeutic efficacy but also reduces the dosing frequency in its sustained release fashion. The desired PS of 143.6 nm, ZP 19.1 mV, and high EE of 88.31% were achieved. Our recommendations are lyophilized powder filled into the hard gelatin capsule for oral delivery for the treatment of PD.

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ABBREVIATIONS

SLN: Solid Lipid Nanoparticles; **PS:** Particle Size; **ZP:** Zeta Potential; **EE:** Entrapment Efficiency; **BBD:** Box-Behnken Design.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

SUMMARY

The patients suffering from Parkinson disease require immediate attention and the existence of a drug in the body. The agents useful in Parkinson disease given by the conventional route show various limitations in the therapy. Hence, to overcome these issues, solid lipid nanoparticles are one of the best options. SLN-loaded Entacapone not only enhances the bioavailability and therapeutic efficacy but also delivers the drug in a sustained manner for 12 hr. SLN shows a dual release pattern, which is needed for the patient suffering from PD. The PS 143.6 nm, ZP 19.1 mV, and high EE of 88.31%, and stability achieved in SLN-loaded entacapone.

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