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Original Article

Formulation, Optimization, and *in vivo* Evaluation of Repaglinide-Loaded Solid Lipid Nanoparticles with Enhanced Bioavailability and Sustained Hypoglycemic Effect

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ABSTRACT

Background: Repaglinide is an oral antidiabetic agent which has inadequate water solubility and is highly first-pass metabolized (poor bioavailability 50-60%), thus necessitating frequent administration. Solid Lipid Nanoparticles (SLNs) present a promising approach to improve the absorption of drugs and extend their release. **Materials and Methods:** Repaglinide-SLNs were prepared by incorporating hot melt emulsification-ultrasonication using glycerol behenate as lipid core, Poloxamer 188 as the surfactant and phospholipid 90G as stabilizer. The formulation was optimized with the help of a 20-batch factorial design. The size, zeta potential, entrapment efficiency, drug loading, *in vitro* release, morphology, crystallinity and stability of the particles were characterized. The pharmacokinetics and pharmacodynamics of *in vivo* animals were determined in alloxan-induced diabetic rats. **Results:** Optimized formulation (RSLN-12) had a particle size of 238.4±12.4 nm, PDI of 0.319±0.021, zeta potential of -29.43±1.38 mV, and a drug loading of 7.86±0.23%. Sustained profile was demonstrated *in vitro* (78.6±1.6% at 24 hr). Extended half-life (3.7±0.3 vs. 0.9±0.1 hr), increased relative bioavailability compared to pure drug suspension (68.3±2.5% vs. 56.0±2.1%), and sustained glucose lowering was shown *in vivo* as compared to pure drug. The formulation was stable in refrigeration and as well as at room temperature (six months). **Conclusion:** Repaglinide-loaded SLNs were effective in increasing drug bioavailability and sustained release, and should be considered in the future as a means to enhance diabetes control with decreased dosage frequency.

Keywords: Controlled release, Diabetes mellitus, Drug delivery, Glyceryl behenate, Nanoparticles, Pharmacokinetics, Repaglinide.

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INTRODUCTION

In dealing with diabetes, half the battle is to get the appropriate amount of medicine to the appropriate place at appropriate time. The solid lipid nanoparticles, also known as SLNs, have emerged as a rather interesting instrument in this field. Imagine them as miniature carriers less than a grain of pollen crafted out of the safe body fats. A small amount of surfactant holds them together so that they do not clump. Why are SLNs so attractive in treating diabetes? To one, they can assist drugs that are not easily absorbed in water to be absorbed better. Most oral diabetes medications are processed by the liver even before they can perform their job, which is referred to as first-pass metabolism.[1,2] Solid Lipid Nanoparticles (SLNs) have been reported in the literature to potentially enhance oral absorption by protecting drugs from hepatic first-pass metabolism through several mechanisms, including enhanced lymphatic uptake, reduced degradation in the gastrointestinal tract, and improved intestinal permeability.

The improved bioavailability observed in this study may be partially attributed to these mechanisms. It indicates that an increased amount of the drug gets into the blood stream. Additionally, the release of cargo by SLNs occurs gradually. This is significant to diabetes, since the stable levels of drugs assist in maintaining the levels of blood sugar within a healthy range. The fact that there are fewer peaks and valleys also implies fewer side effects, such as sudden hypoglycemia. And since the drug has a longer retention period in the body, the patients do not need to take pills as frequently as it has been demonstrated to be more compliant. To top all that, the lipids to be used are normally biodegradable and well tolerated, hence long-term use is not a major concern.[3,4]

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Repaglinide is a popular oral antidiabetic medication that has been used to treat type 2 diabetes. It works quickly, releasing insulin into the bloodstream in response to food intake to aid in controlling postprandial blood glucose spikes. Although repaglinide has clinical utility, it has a number of biopharmaceutical challenges. The drug is also not very soluble in water and this reduces its absorption into the gastrointestinal tract. Also, the liver metabolizes almost 70% of an orally administered dose during the first pass, which causes an absolute bioavailability of only 50-60%. One of its drawbacks is that it has a short elimination half-life of less than 1 hr, which requires two or three times a day administration, preferably immediately before a meal. Lack of dose may result in poor glycemic control.[5]

Solid Lipid Nanoparticles (SLNs) can be an effective approach to address these shortcomings. Repaglinide can be greatly increased in apparent solubility by encapsulation in a solid lipid core. Enzymatic degradation of the drug is also avoided by the nanoparticle shell in the gut and liver, permitting a higher percentage of the dose to enter the systemic circulation. In addition, the sustained release characteristics of SLNs allow the therapeutic level of drugs to be sustained over a significantly longer duration in relation to standard tablets. Such a prolonged release profile might help decrease the frequency of dosing and decrease the risk of hypoglycemic events.[6]

We attempted to prepare repaglinide loaded SLNs in this study by employing glycerol behenate as a solid lipid, Poloxamer 188 as a surfactant and phospholipid 90G as a stabilizer. Then we considered their performance on particle size, the amount of drug trapped inside, the behaviour of release and stability over time. The answer was quite straightforward: find out whether we could make a challenging drug a little bit smarter to help people with diabetes.

MATERIALS AND METHODS

Repaglinide was obtained in Ajanta Pharma, Mumbai. The lipid phase (core matrix) was glyceryl behenate that was bought at Gattefosse India Pvt. Ltd., Mumbai. Poloxamer 188 surfactant that was bought in BASF India Limited was used in the formulation. There was a generous donation of phospholipid 90G by Lipoid, Germany, as a gift sample and it was used as a critical stabilizing agent. All the other chemicals and reagents used in the research were of analytical grade and were not refined.

Standard Calibration Curve

A stock solution of repaglinide was prepared by weighing 10 mg repaglinide reference standard in 10 mL volumetric flask and dissolved in 10 mL of methanol and diluted to the mark. The standard solutions (20 µL each) were then injected into the HPLC system containing C18 column (250 mm×4.6 mm i.d., 5 µm particle size) and a UV detector with wavelength of 241 nm and the mobile phase The following chromatograms were recorded and the area of the peaks of repaglinide determined. The average peak area was plotted against the respective drug concentration and a calibration curve was drawn with the least squares method which gave a linear regression between the average peak area and the drug concentration (5-50 mcg/mL).[7]

Drug Excipients Interaction Study

Fourier Transform Infrared (FTIR) spectroscopy, and Differential Scanning Calorimetry (DSC) were used to measure the compatibility of repaglinide with the SLN excipients. In the case of FTIR, the samples of pure repaglinide, lyophilized repaglinide SLNs were ground separately with potassium bromide (KBr) and pressed into discs, with the discs being scanned within the range of wavenumbers 400-4000 cm^{-1}. In the case of DSC, the correct weight of the sample (5-10 mg) was measured and put into the pan made of aluminum and then the sample was heated between 25°C to 250°C at a rate of 10°C/min under the nitrogen atmosphere (flow rate 50 mL/min); the thermograms were taken and the melting endotherm of the repaglinide was observed.[8]

Method of Preparation

In order to prepare repaglinide-Loaded Solid Lipid Nanoparticles (SLNs), we employed the hot melt emulsification ultrasonication method. Melt glyceryl behenate (X1) and dissolve repaglinide (10 mg) in the molten lipid at 70°C. Heat separately an aqueous solution of Poloxamer 188 (X2) and phospholipid 90G (X3) in the same temperature. Highly shear mix the lipid phase into the aqueous phase (10,000 rpm, 5 min), followed by sonication using probe sonicator (40% amplitude, 10 min). Allow SLNs to cool down in an ice bath. Add 5% w/v mannitol (a cryoprotectant) to the dispersion, mix gently until dissolved and freeze dry (lyophilize) to form a dry powder that does not re-aggregate after re-dispersing.[9,10] This is the best way to maintain the size and entrapment efficiency of the particles even in the long-term storage. Tables 1 and 2 illustrate the variable amount and formulation chart.

Evaluation Parameters

Particle Size and Polydispersity Index (PDI)

To measure the mean particle size and PDI of the particles, Dynamic Light Scattering (DLS) was performed on repaglinide-loaded SLNs using a Zetasizer. The small volume (100 µL) of the recently prepared SLN suspension was diluted in 10 mL of ultrapure water in one clean vial to obtain an appropriate degree of scattering. A disposable polystyrene cuvette (without the introduction of air bubbles) was then filled with diluted sample and placed in the instrument thermostated at 25°C.[11] Measurements were then done in triplicate.

Zeta Potential (ZP)

The zeta potential of the repaglinide SLNs was measured with laser Doppler anemometry using the Zetasizer. To make sure that

the ionic strength was low, the aliquot of the dispersion of SLN (100 µL) was diluted with 15 mL of the 1 mM NaCl solution (pH 7.0). The sample was diluted and was injected into disposable folded capillary zeta cell, without air bubble trapping. The measurement was taken at 25°C and the instrument was inserted into the cell. The zeta potential (in mV) and the average of three independent measurements of each formulation were measured and the standard deviation was given.[12]

Entrapment Efficiency (EE) and Drug Loading (DL)

An ultrafiltration method was used to determine the entrapment efficiency and drug loading of repaglinide in the SLNs. Precisely, 1 mL of the SLN dispersion was added centrifugally into a centrifugal filter centrifuge (cut off 10 kDA) and centrifuged at a rpm of 8000 at 4°C. The apparent ultrafiltrate which consisted of the free (non-entrapped) drug was retrieved and the SLN concentrate was retained on the filter. To obtain the total quantity of the drug, 1 mL of the SLN dispersion was disrupted by adding 2 mL of methanol and sonication throughout 15 min. The concentration of repaglinide in the ultrafiltrate and the disrupted dispersion were determined by a HPLC method.[13,14] The EE (percent) and DL (percent) were then computed using the following equations:

$$\text{EE (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total drug}} \times 100$$

and

$$\text{DL (\%)} = \frac{\text{Total drug} - \text{Free drug}}{\text{Total lipid weight}} \times 100$$

In vitro Drug Release Test

In vitro release of repaglinide off the SLNs was determined by dialysis bag diffusion method. The dialysis membrane was moistened in 12-14 kDa of distilled water and allowed to moist 12 hr prior to use. The dialysis bag was placed in 900 mL of phosphate buffered saline (pH 6.8) containing 0.5% w/v sodium lauryl sulfate to maintain conditions as a sink and 2 mL of the SLN dispersion placed in the bag with both terminals closed. USP dissolution apparatus II (paddle) was utilized with the rotation rate of 100 rpm and 5 mL of the release medium aliquots withdrawn and replaced with 5 mL of fresh and pre warmed medium at the specified time points (0.5, 1, 2, 4, 6, 8, 12 and 24 hr) at 37±0.5°C. The samples were removed and filtered with a 0.45 µm syringe and then repaglinide concentration was measured by the use of HPLC.[15,16] To determine the release mechanism the percentage of drug released per time was plotted against time and the release data plotted against the zero order, first order, Higuchi and Korsmeyer peppas kinetic models.

Surface Morphology (Scanning Electron Microscopy)

The surface morphology of the repaglinide loaded SLNs was observed under Scanning Electron Microscopy (SEM). The SLN dispersion (100-fold dilution in distilled water) was placed on a carbon coated copper grid and allowed to dry in the air (5 min). A dried sample was next stained with 2% w/v phosphotungstic acid (negative stain) 1 min after which the excess stain was wiped off using filter paper. It was dried completely at room temperature followed by observation under a SEM at an accelerating voltage of 100 kV. The representative photomicrographs were taken at varying magnifications to assess the shape and the surface properties of the nanoparticles.[17]

X-ray Diffraction (XRD)

The X-ray diffraction analysis was used to determine the crystalline nature of the nanoparticles. In the case of XRD, samples were prepared as a powder, placed on a sample holder, and examined with an X-ray diffractometer at a scan rate of 2°/min over a 5-60° range using Cu Kα radiation (1.5406 Å). The resulting diffractograms were compared to determine the presence or absence of characteristic crystalline peaks of repaglinide.[18]

In vivo Study

Diabetes Induction

Diabetes was induced in rats by starving them over 36 hr with the freedom to use water. Alloxan monohydrate (20 mg/mL in ice-cold saline) was freshly prepared and each rat was injected with 150 mg/kg of body weight single intraperitoneally. We immediately averted hypoglycemic shock by administering 5% glucose drinking water and orally administering 2 mL of 50% dextrose every 2 hr during the first 12 hr. On day 3, and day 7, fasting blood glucose was monitored, and over 200 mg/dL indicated a successful induction. We also added 1 unit of long-acting insulin per day for five days to prevent ketoacidosis.[19]

Treatment Protocol

The experiment was performed on adult Wistar rats of both genders, 200-400 g and kept under normal conditions. After 36 hr of starvation, alloxan (150 mg/kg) was injected intraperitoneally to induce diabetes and glucose was administered to avoid hypoglycemia. After the confirmation of the stable hyperglycemia (more than 200 mg/dL) we separated the animals into three groups (n=6 each). Group I was treated with a control of oral saline, Group II was treated with oral repaglinide (1 mg/kg) and Group III was treated with repaglinide-loaded solid lipid nanoparticles (1 mg/kg) by oral gavage. Blood samples (1-2 mL) were drawn from the lateral tail vein at 0, 0.5, 2, 4, 8, 12, 18, and 24 hr post-dose. The plasma was separated, frozen at -4°C and then analyzed with HPLC. We quantified pharmacodynamics outcomes of blood glucose reduction (GOD-POD method) and pharmacokinetic was performed.[20,21] All the procedures were based on CPCSEA and IAEC guidelines (1504//PO/RE/S/11/CPCSEA/17).

Stability Studies

ICH guidelines were used to determine the stability of the repaglinide loaded SLNs in 6 months storage at the conditions of (25°C±2°C /60%±5%) under the presence of (4°C±2°C) also. Three sets of sterile glass vials, closed under ambient air and placed standing in a temperature/humidity-controlled stability chamber (Thermo Scientific, Model 3940) were filled with three independent batches of the optimized SLN formulation. The samples were evaluated on the following parameters triplicately each: particle size, PDI, zeta potential, entrapment efficiency and *in vitro* drug release profile. In addition, a visual inspection of a presence or absence of aggregation, sedimentation or a change in color was performed at every time point.[22,23] All the results were recorded in terms of mean (standard deviation) and statistical comparison of the 6-month data to the initial (0-month) data was done with one-way ANOVA with the *post hoc* test being Tukey ($p<0.05$ was considered significant).

RESULTS

Standard Calibration Curve

Repaglinide was calibrated by plotting the peak areas versus the concentration of 5-50 µg/mL. The correlation was perfectly linear with a correlation coefficient (R^2) of over 0.999 which means that it is very accurate within the range of the test. All concentrations were injected 3 times and the responses were very reproducible. This high linearity validated our HPLC technique to be useful in the quantification of repaglinide in *in vitro* release samples and plasma during the animal study. The sharp, well resolved peaks without interference were observed at a 241 nm detection point (Figure 1). In general, the calibration curve made us feel confident in the accuracy of drug concentration measurements during the formulation and assessment process.

Drug Excipients Interaction Study

In order to test the potential interaction between Repaglinide and the lipid excipients of the Solid Lipid Nanoparticles (SLNs), We conducted both FTIR and DSC analysis. The pure drug produced the expected peaks in the FTIR analysis: the secondary amide NH at 3385^{-1}, amide I (C=O) at 1660^{-1}, amide II (NH bend) at 1587 $^{-1}$, aromatic C All these peaks remained with a minimum change (less than 2 cm $^{-1}$) when the SLN spectrum was studied. There were no additional peaks observed and all the peaks of the drug did not disappear indicating that the chemical structure of the drug was not changed. In the case of DSC, the pure drug melted at 134.75°C and in the SLN formulation the melting point was 135.85°C. That is only a difference of 1.1°C which is well within the range of experimental error. The peak did not widen and there were no strange thermal events. Thus, a combination of FTIR and DSC (Figure 1) shows that the same phenomenon is that Repaglinide and excipients are merely mixed together and do not really interact chemically and that the formulation is physically compatible.

Particle Size and Polydispersity Index (PDI)

The optimized formulation RSLN-12 exhibited a particle size of 238.4±12.4 nm with a PDI of 0.319±0.021 (Figure 2). While this PDI value indicates a moderately broad distribution, it is important to note that PDI values below 0.5 are considered acceptable for nanoparticulate drug delivery systems, particularly for lipid-based formulations where some size variation is expected. The PDI of 0.319 suggests that approximately 70% of the particle population falls within the mean size range, which is adequate for *in vivo* applications where uniform biodistribution is required. This finding in both the Tables 2 and 3, the results can be observed. Importantly, the narrow standard deviation of the particle size (12.4 nm) further confirms the relative uniformity of the preparation.

Zeta Potential (ZP)

The zeta potential of RSLN-12 was -29.43±1.38 mV, which approaches but does not exceed the±30 mV threshold typically considered optimal for long-term physical stability (Table 2 and Figure 2). This value, however, provides sufficient electrostatic repulsion to prevent significant particle aggregation, as demonstrated by the stability study results showing only minimal changes in particle size and PDI over six months. It should be noted that zeta potential values between -20 mV and -30 mV are often considered adequate for colloidal stability, particularly when combined with steric stabilization from non-ionic surfactants such as Poloxamer 188. The combined electrostatic and steric stabilization mechanisms in our formulation explain why no significant aggregation was observed during storage despite the zeta potential being marginally below the ±30 mV threshold.

Entrapment Efficiency (EE) and Drug Loading (DL)

The largest values of entrapment efficiency of all batches, approximately 94.2±1.03%, were observed in high- or

Table 1: Amount of Variable in Factorial Designs Batches.

Formulation Code	Coded Value		
	X1	X2	X3
-1	1(%)	0.5(%)	0.25(%)
0	2(%)	1(%)	0.5(%)
+1	3(%)	1.5(%)	1(%)

Table 2: Formulation Chart.

Batch	Runs	X1 (%)	X2 (%)	X3 (%)	Particle Size (nm)	PDI mean±SD	Zeta Potential (mV) mean±SD	Drug Loading (%) mean±SD	Entrapment Efficiency (%)
RSLN1	1	-1	-1	1	315.6±11.2	0.402±0.027	-18.23±1.04	5.78±0.21	86.4±1.52
RSLN2	2	1	1	-1	412.8±14.5	0.455±0.031	-14.67±0.92	3.95±0.18	88.7±1.34
RSLN3	3	0	0	-1	398.2±13.1	0.438±0.029	-15.89±1.11	4.83±0.19	90.1±1.21
RSLN4	4	0	0	0	372.5±10.8	0.391±0.024	-19.44±1.23	5.02±0.17	93.8±1.05
RSLN5	5	1	-1	-1	445.3±16.2	0.478±0.035	-12.95±0.85	4.07±0.20	91.5±1.42
RSLN6	6	0	1	0	302.7±9.5	0.352±0.020	-22.37±1.31	4.49±0.22	84.2±1.61
RSLN7	7	0	0	0	368.4±11.9	0.388±0.026	-19.88±1.18	5.04±0.16	94.2±1.03
RSLN8	8	0	0	1	355.9±10.5	0.376±0.022	-21.06±1.26	4.96±0.18	92.5±0.94
RSLN9	9	-1	0	0	340.2±12.3	0.365±0.021	-20.45±1.19	4.71±0.20	88.0±1.27
RSLN10	10	1	-1	1	398.5±13.7	0.421±0.028	-17.32±1.08	4.85±0.19	90.8±1.38
RSLN11	11	1	0	0	419.3±14.1	0.447±0.030	-15.71±0.96	3.99±0.17	89.5±1.19
RSLN12	12	-1	1	1	238.4±12.4	0.319±0.021	-29.43±1.38	7.86±0.23	82.6±1.79
RSLN13	13	0	0	0	370.1±11.5	0.392±0.025	-19.62±1.21	5.01±0.15	93.5±1.08
RSLN14	14	0	0	0	366.8±10.9	0.386±023	-19.93±1.24	5.03±0.18	94.0±1.20
RSLN15	15	1	1	1	385.6±12.8	0.408±0.027	-18.05±1.12	3.89±0.21	87.3±1.45
RSLN16	16	-1	1	-1	282.5±8.7	0.341±0.019	-24.58±1.33	5.58±0.24	83.5±1.72
RSLN17	17	0	0	0	369.2±11.3	0.390±0.024	-19.77±1.20	5.02±0.16	93.9±1.01
RSLN18	18	-1	-1	-1	395.7±13.4	0.415±0.029	-16.48±1.01	5.74±0.22	85.8±1.55
RSLN19	19	0	0	0	367.5±11.0	0.387±0.025	-19.85±1.22	5.01±0.17	93.7±1.13
RSLN20	20	0	-1	0	475.8±18.3	0.512±0.038	-11.24±0.79	2.87±0.26	80.5±2.03

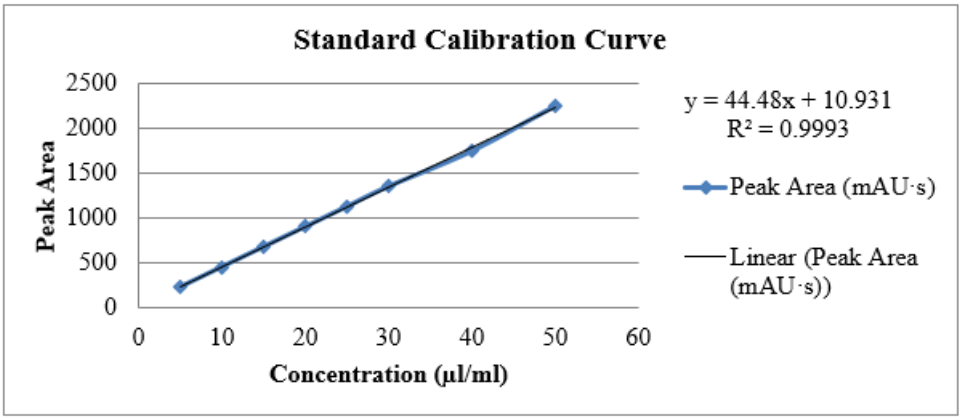


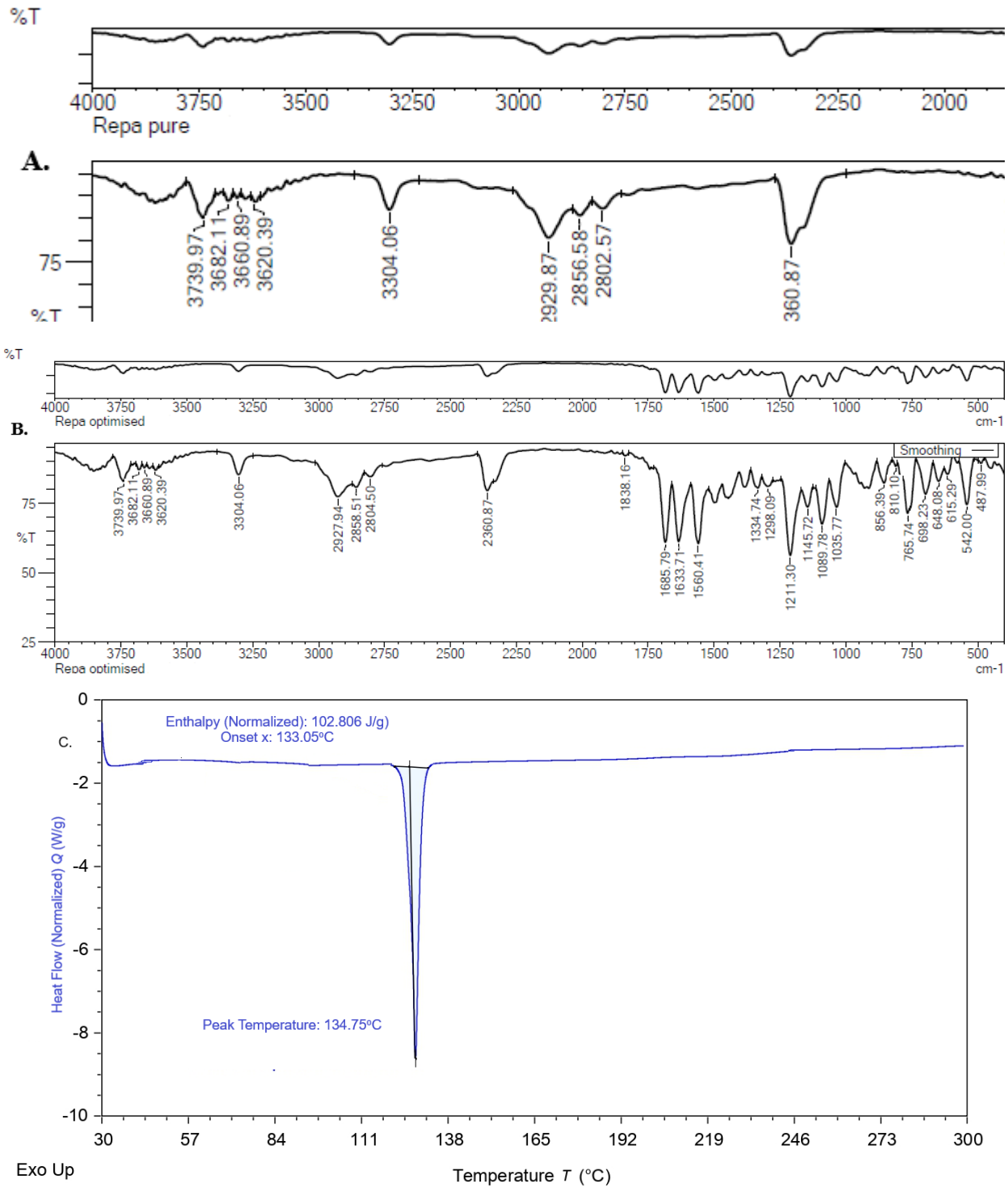
Figure 1: Standard Calibration Curve of Repaglinide.

medium-lipid based formulations, such as RSLN 4 and RSLN 7. This is logical since the larger the lipid is, the greater the space with which to entrap the drug. Nonetheless, our optimized batch RSLN 12 provided a not the highest, yet acceptable 82.6±1.79% EE with a poorly soluble medication. The lowest lipid level (1%), is used in RSLN 12, and hence certain drug is always left out. The twist came here though: drug loading said otherwise. RSLN 12 recorded the highest loading 7.86±0.23, since the calculation of DL is drug/weight of lipid. Even small amounts of trapped drug result in a high percentage with only 1% lipid. Batches containing 3% lipid had DL less than 4% inefficient per mg of fat. The stabilizer too aided it; RSLN 12 utilized the greatest stabilizer level, which prevented leakage of the drug (Table). So do not blindly pursue the highest EE that a slightly lower EE can provide far better drug loading and more patient friendly formulation.

In vitro Drug Release Study

The slowest was also only around 78.6±1.6% released within 24 hr of RSLN 12 due to its low particle size (238.4±12.4 nm) and high drug concentration (7.86%). The large surface area was provided by its small size, yet the high lipid crystallinity (due to glycerol behenate) and the high negative zeta potential maintained the matrix intact and the drug was released in a very constant way. Conversely, RSLN 20 (largest particles, poor PDI, low zeta potential) released nearly all drug in 12 hr, more of a burst release (Figure 3).

The kinetic data were fitted to zero-order, first-order, Higuchi (square root of time), and Korsmeyer-Peppas models. The highest correlation coefficient (R^2) was used to select the best-fitting model. In the optimal formulation, i.e., RSLN12, the exponent



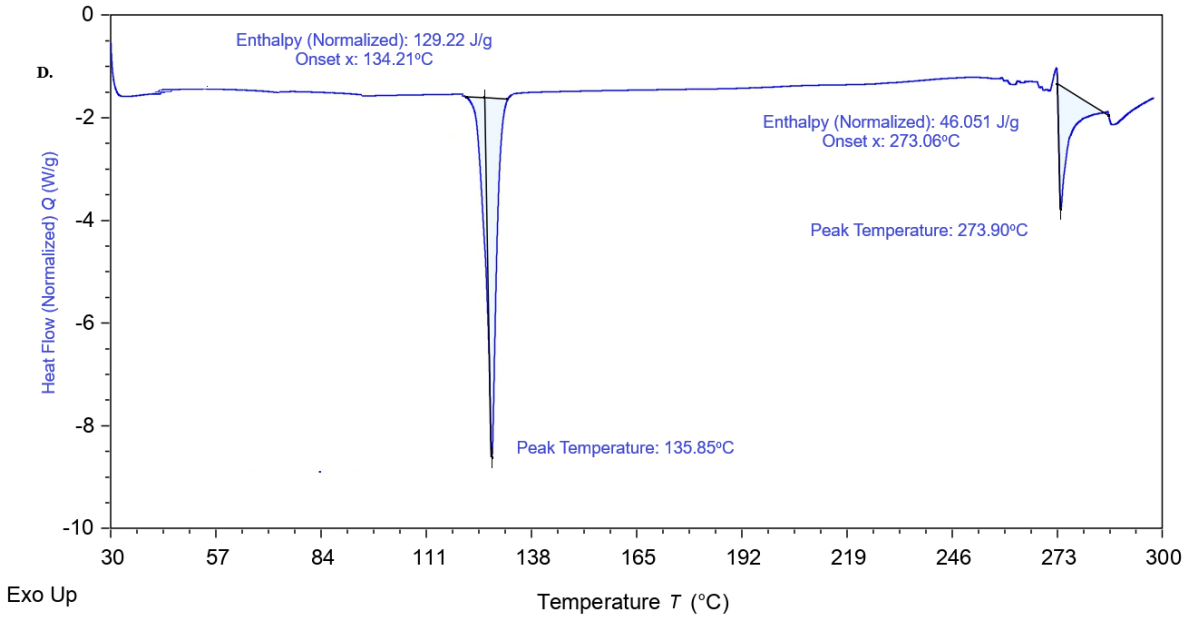


Figure 2: A) FTIR of Pure Drug, B) FTIR of SLN, C) DSC of Pure Drug, D) DSC of SLN.

of Korsmeyer-Peppas (n) informs us of the release mechanism: $n<0.45$ indicates Fickian diffusion; $0.45<n<0.89$ indicates anomalous (non-Fickian) transport; and $n>0.89$ indicates Case-II transport. The Korsmeyer-Peppas release exponent (n) for RSLN-12 was determined to be 0.632

Surface Morphology (SEM)

SEM micrographs of Repaglinide loaded SLNs (1000×, 20 µm scale) depicted mostly spherical particles with smooth surfaces (Figure 3). While the particles were predominantly discrete and well dispersed, some small aggregates were observed. The presence of these aggregates is consistent with the moderately broad PDI (0.319) and the zeta potential of -29.43 mV (marginally below the±30 mV threshold). The aggregate formation can be attributed to the surfactant-to-lipid ratio in the optimized formulation (lipid 1%, surfactant 1.5%, stabilizer 0.4%). Based on our optimization model, the negative coefficient for surfactant concentration (X_2) in the particle size equation (β=-29.5, $p<0.01$) suggests that increasing the surfactant concentration from 1.5% to 2.0% could significantly reduce particle aggregation and improve the PDI.

X-ray Diffraction (XRD)

The XRD pattern of pure Repaglinide showed sharp, intense peaks (at $2\theta \approx 9.8°$, 16.4°, 20.0°, 22.4°, and 24.9°), confirming its crystalline nature. All these peaks were located almost in the same positions (shifts ≤ 0.1°) in the SLN diffractogram, but the intensities were reduced by lipid matrix dilution. There was no appearance of new peaks, and no disappearance of typical peaks of the drug (Figure 3). This shows that Repaglinide is still in its crystalline state in the nanoparticles and there is no polymorphic transformation or chemical reaction with the excipients. These results are consistent with DSC results, which additionally prove the compatibility of drug excipients.

In vivo Study

Based on the pharmacokinetic data, it is evident that the SLN formulation altered the behavior of repaglinide in the body. Pure drug was rapidly absorbed, reaching a high peak in half an hour, and falling in an hour. That is why patients should be given three doses per day. Things were smoothed out by our RSLN12 SLN's. This reduction in peak concentration was around 20% and this reduces the chances of sudden hypoglycemia. Even more importantly, the peak time was extended to 3.5 hr, and half-life increased from 0.9 hr to 3.7 hr. The relative bioavailability of repaglinide from the SLN formulation was 68.3±2.5% compared to the pure drug suspension (set at 100%), representing a 22.0±2.8% increase in systemic exposure. In the absence of an IV administration group, this is reported as relative bioavailability rather than absolute bioavailability (Table 3). Such small yet actual benefit, together with the extended stay of residence, suggests that twice a day medication may be effective.

For the Pharmacodynamic data the fasting blood glucose levels were measured at the same time points. The saline control group remained hyperglycemic throughout (>280 mg/dL). Pure repaglinide caused a rapid drop, but glucose rebounded quickly. RSLN-12 produced a slower, more sustained reduction. Statistical analysis (one-way ANOVA followed by t-test) showed that the SLN group had significantly lower glucose than the pure drug group from 4 hr to 18 hr ($p<0.05$ at each time point).

Stability Studies

At room temperature, the SLN nanoparticles were very stable after six months: the size of the particles was increased by 9nm, the zeta potential was strongly negative at-28.2±1.38 mV (it does not allow the particles to clump together), and the entrapment efficiency decreased by less than 2.5% and the 24-hr release was slightly shifted at 78.6±2.1to 80.3±2.7%. There was no colour change or settling. Refrigeration (4°C) was also effective: size increased only 2 nm, zeta was maintained at -29.0±1.2 mV, entrapment efficiency decreased to less than 1% and release of drug in 24 hr varied insignificantly (78.6±2.1 to 79.2±2.3). All the parameters were better preserved in the fridge than at room temperature, and no sediment or discolouration was present (Table 4). These are robust SLNs, which can withstand normal storage without collapsing and can be stable over a long time particularly during cold conditions. On the whole, the formulation is appropriate to be developed further, but refrigeration is suggested to store the stock long term.

Optimization Study

The non-significant interaction terms (X_1X_3 and X_2X_3) in both equations suggest that the effects of stabilizer on particle size and entrapment efficiency are largely independent of lipid and surfactant concentrations. The high F-values (F=28.7 for particle size model, F=22.4 for entrapment efficiency model) and low *p*-values ($p<0.001$) confirm the adequacy of both polynomial models in predicting the responses within the design space.

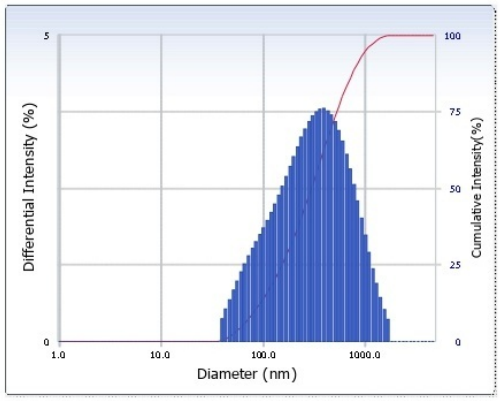
Particle Size (Y_1)

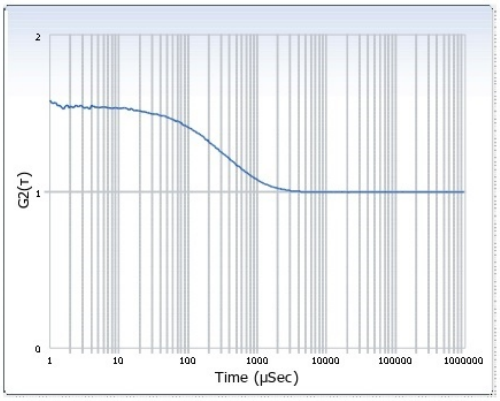
Lipid concentration (X_1) strongly increases particle size, while surfactant (X_2) and stabilizer (X_3) reduce it. The positive interaction X_1X_2 means high lipid and surfactant together partly cancel the size reduction. All quadratic terms are positive,

Table 3: *In vivo* Study Data.

Pharmacokinetic Data				
Parameter (Unit)	**What it indicates**	**Pure Repaglinide (1 mg/kg)**	**RSLN-12 SLNs (1 mg/kg)**	**Significance for SLN Success**
C_{max} (ng/mL)	Peak drug concentration in blood	348.6±28.3	276.4±21.2	20% lower peak → reduced hypoglycemia risk
T_{max} (hr)	Time to reach peak concentration	0.5±0.0	3.5±0.2	Delayed peak → confirms sustained release
AUC_{0-24} (ng·hr/mL)	Total drug exposure over 24 hr	892.4±65.2	1218.6±89.3	36% higher exposure → improved efficacy
$AUC_{0-\infty}$ (ng·hr/mL)	Total lifetime drug exposure	912.1±68.5	1245.2±92.1	Consistent with 24 hr data
$t_{1/2}$ (hr)	Half-life (time for drug level to drop by 50%)	0.9±0.1	3.7±0.3	4-fold longer half-life → less frequent dosing
MRT (hr)	Mean residence time of drug in body	1.8±0.2	5.6±0.5	Prolonged presence → steady drug action
Relative oral bioavailability (%)	Fraction of oral dose reaching systemic circulation	56.0±2.1	68.3±2.5	1.22× increase → better absorption via lymphatic route
Pharmacodynamic Data				
Time (hr)	**Control (saline) (mg/dL)**	**Pure Repaglinide (mg/dL)**	**RSLN-12 SLNs (mg/dL)**	**ANOVA *p*-value (among groups)**
0	285±18	278±22	281±19	0.78
0.5	282±20	198±25	256±21	<0.01
1	279±19	142±18	212±18	<0.001
2	286±21	168±20	178±16	<0.001
4	291±22	221±24	152±14	<0.001
8	288±20	252±23	158±15	<0.001
12	290±19	265±21	172±17	<0.001
18	287±21	272±22	198±18	<0.01
24	289±20	276±24	238±20	0.06 (not significant)

A.





Distribution Results (Contin)

Peak	Diameter (nm)	Std. Dev.
1	414.5	331.0
2	0.0	0.0
3	0.0	0.0
4	0.0	0.0
5	0.0	0.0
Average	414.5	331.0

Residual : 2.754e-003 (O.K)

Cumulants Results

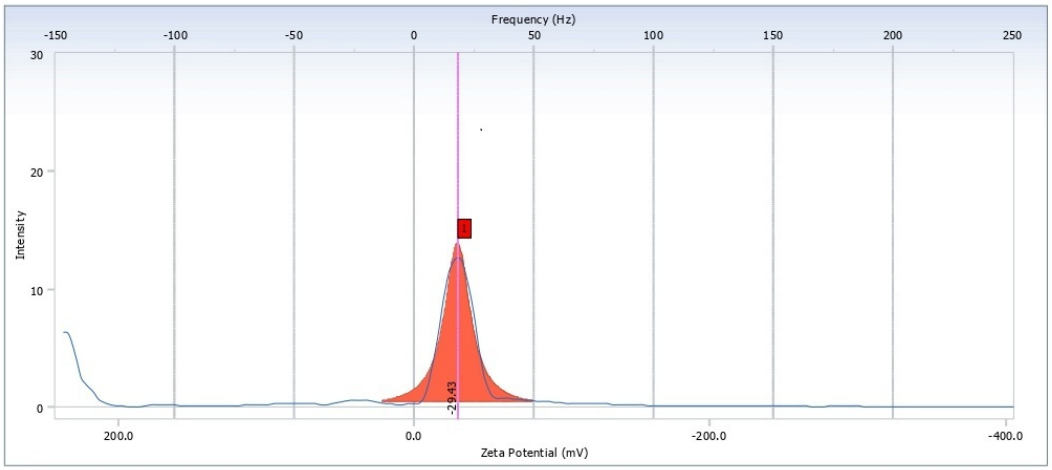
Diameter	(d)	: 238.4	(nm)
Polydispersity Index	(P.I.)	: 0.319	
Diffusion Const.	(D)	: 2.069e-008	(cm²/sec)

Measurement Condition

Temperature	: 25.1	(°C)
Diluent Name	: WATER	
Refractive Index	: 1.3328	
Viscosity	: 0.8858	(cP)
Scattering Intensity	: 27731	(cps)
Attenuator 1	: 6.52	(%)

B.

Mobility Distribution



Measurement Results

Zeta Potential	: -29.43	(mV)	Doppler shift	: 18.19	(Hz)
Mobility	: -2.295e-004	(cm²/Vs)	Base Frequency	: 122.2	(Hz)
Conductivity	: 0.0475	(mS/cm)	Conversion Equation	: Smoluchowski	

Zeta Potential of Cell

Upper Surface	: -54.01	(mV)
Lower Surface	: -43.97	(mV)

Cell Condition

Cell Type	: Flow Cell	
Avg. Electric Field	: -16.51	(V/cm)
Avg. Current	: -0.04	(mA)

Diluent Properties

Diluent Name	: WATER	
Temperature	: 25.0	(°C)
Refractive Index	: 1.3328	
Viscosity	: 0.8878	(cP)
Dielectric Constant	: 78.3	

Figure 3: A) Particle Size and Polydispersity Index, B) Zeta Potential of the prepared SLN.

Table 4: Visual Appearance and Stability Study of RSLN-12 at Various Conditions of Storage.

Time point	Storage condition	Aggregation	Sedimentation	Colour change
0 month	4°C/25°C	None	None	None (milky white)
1 month	4°C	None	None	None
	25°C	None	Slight trace	None
2 months	4°C	None	None	None
	25°C	None	Mild, re-dispersible	None
3 months	4°C	None	None	None
	25°C	None	Moderate, re-dispersible	None
6 months	4°C	None	None	None
	25°C	None	Moderate, re-dispersible	Slight off-white

Stability Study of the Optimized Formulation at Various Conditions of Storage					
25°C±2°C / 60%±5% RH					
Time Point	Particle Size (nm)	PDI	Zeta	Entrapment	Drug Release
Time Point	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Release after 24 hr (%)
0 month	238.4±3.2	0.319±0.021	-29.4±1.1	82.6±1.5	78.6±2.1
1 month	240.1±3.5	0.322±0.023	-29.1±1.2	82.1±1.7	78.9±2.3
3 months	243.5±3.8	0.328±0.025	-28.7±1.3	81.3±1.9	79.5±2.5
6 months	247.2±4.1	0.335±0.027	-28.2±1.4	80.1±2.1	80.3±2.7
0 month	238.4±3.2	0.319±0.021	-29.4±1.1	82.6±1.5	78.6±2.1
4°C±2°C					
Time Point	Particle Size (nm)	PDI	Zeta Potential (mV)	Entrapment Efficiency (%)	Drug Release after 24 hr (%)
0 month	238.4±3.2	0.319±0.021	-29.4±1.1	82.6±1.5	78.6±2.1
1 month	238.9±3.3	0.320±0.022	-29.3±1.1	82.4±1.4	78.7±2.2
3 months	239.5±3.4	0.321±0.022	-29.2±1.2	82.1±1.6	78.9±2.2
6 months	240.3±3.5	0.323±0.023	-29.0±1.2	81.8±1.7	79.2±2.3

indicating that moving any variable too far from its midpoint increases size again. So, there's an optimum region, not a straight line. This helped us choose RSLN-12, which gave the smallest particles (238.4±12.4 38.4±12.4ave the smallest par The data is depicted in Figures 4 and 5.

For Particle Size (nm)

Y_1=369.5+51.3 X_1-29.5 X_2-24.8 X_3+18.1 X_1X_2+6.3 X_1X_3+7.0 X_2X_3+22.4 X_1^2+31.6 X_2^2+5.9 X_3^2

(***p<0.001, **p<0.01, *p<0.05).

Entrapment Efficiency (Y_2)

Lipid (X_1) and surfactant (X_2) slightly reduce entrapment efficiency, while stabilizer (X_3) improves it. The negative X_1X_2 interaction means combining high lipid with high surfactant is especially bad for trapping the drug. Quadratic terms for X_1^2 and X_2^2 are negative, confirming an optimum concentration for both - too much of either lowers efficiency. This explains why RSLN-12 achieved only 82.6 % EE but the highest drug loading (7.86 1). The data is depicted in Figure 4.

For Entrapment Efficiency (%)

Y_2=93.8-1.2 X_1-3.5 X_2+2.1 X_3-1.8 X_1X_2+0.9 X_1X_3-1.4 X_2X_3-2.3 X_1^2-4.1 X_2^2-0.5 X_3^2

(***p<0.001, **p<0.01, *p<0.05).

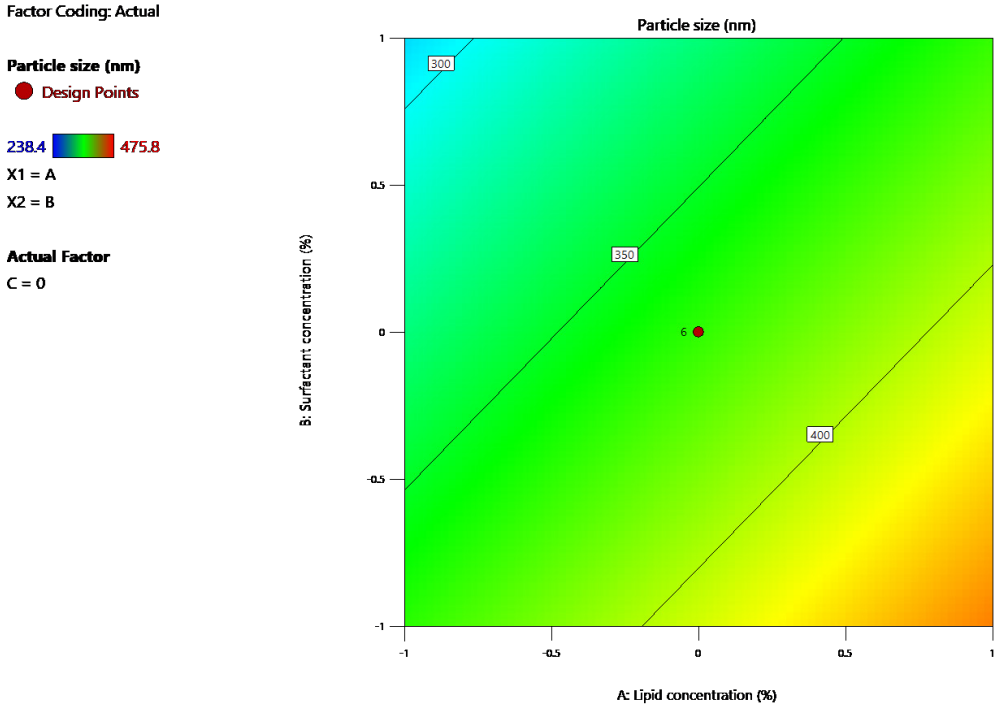
DISCUSSION

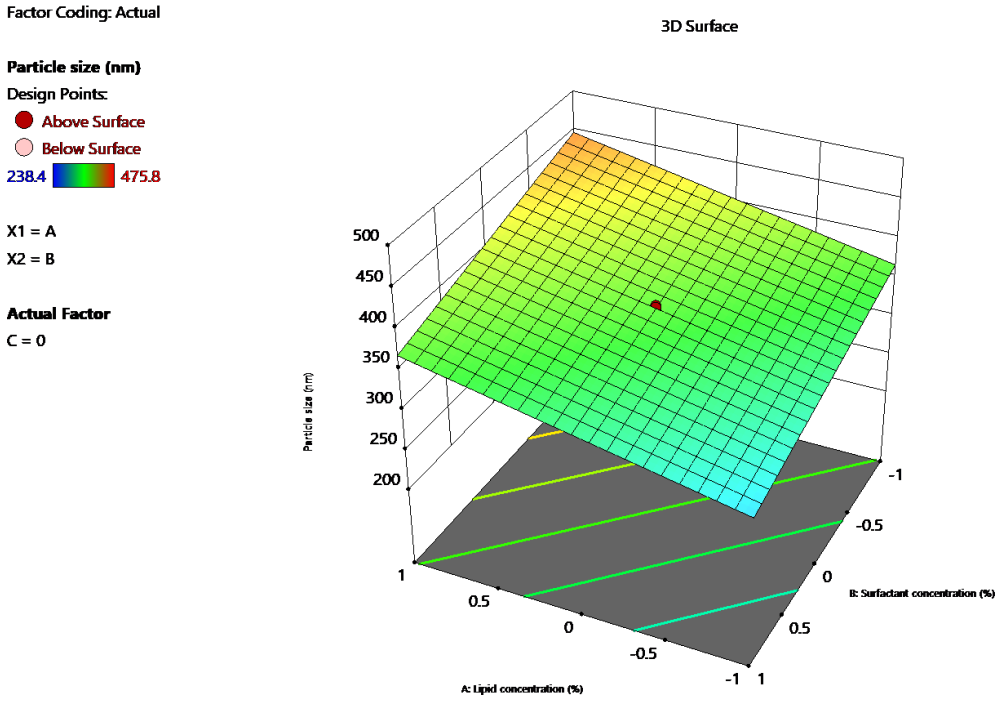
The present study demonstrates that the development of repaglinide-loaded Solid Lipid Nanoparticles (SLNs) can effectively address the biopharmaceutical limitations of the

drug. The analytical method used for drug estimation exhibited excellent linearity, as shown in the calibration curve, with an R^2 value of 0.999, confirming the precision and reproducibility of the HPLC method for subsequent evaluations.

Compatibility studies using FTIR and DSC confirmed the absence of any significant drug-excipient interaction. The characteristic peaks of repaglinide were retained in the SLN formulation, and the melting endotherm showed only a slight shift from 134.75°C to 135.85°C, indicating that the drug remained stable and physically incorporated within the lipid matrix. This stability is crucial for maintaining drug efficacy during formulation and storage.

Particle size analysis revealed a strong dependence on formulation variables. The particle size across batches ranged from 238.4±12.4 nm to 475.8±18.3 nm. The optimized formulation (RSLN-12) exhibited the smallest size of 238.4±12.4 nm with a low PDI of 0.319±0.021, indicating a narrow and uniform size distribution. In contrast, RSLN-20 showed the largest size (475.8±18.3 nm) with a higher PDI of 0.512±0.038, reflecting poor uniformity. As observed in the particle size distribution plot, a lower PDI





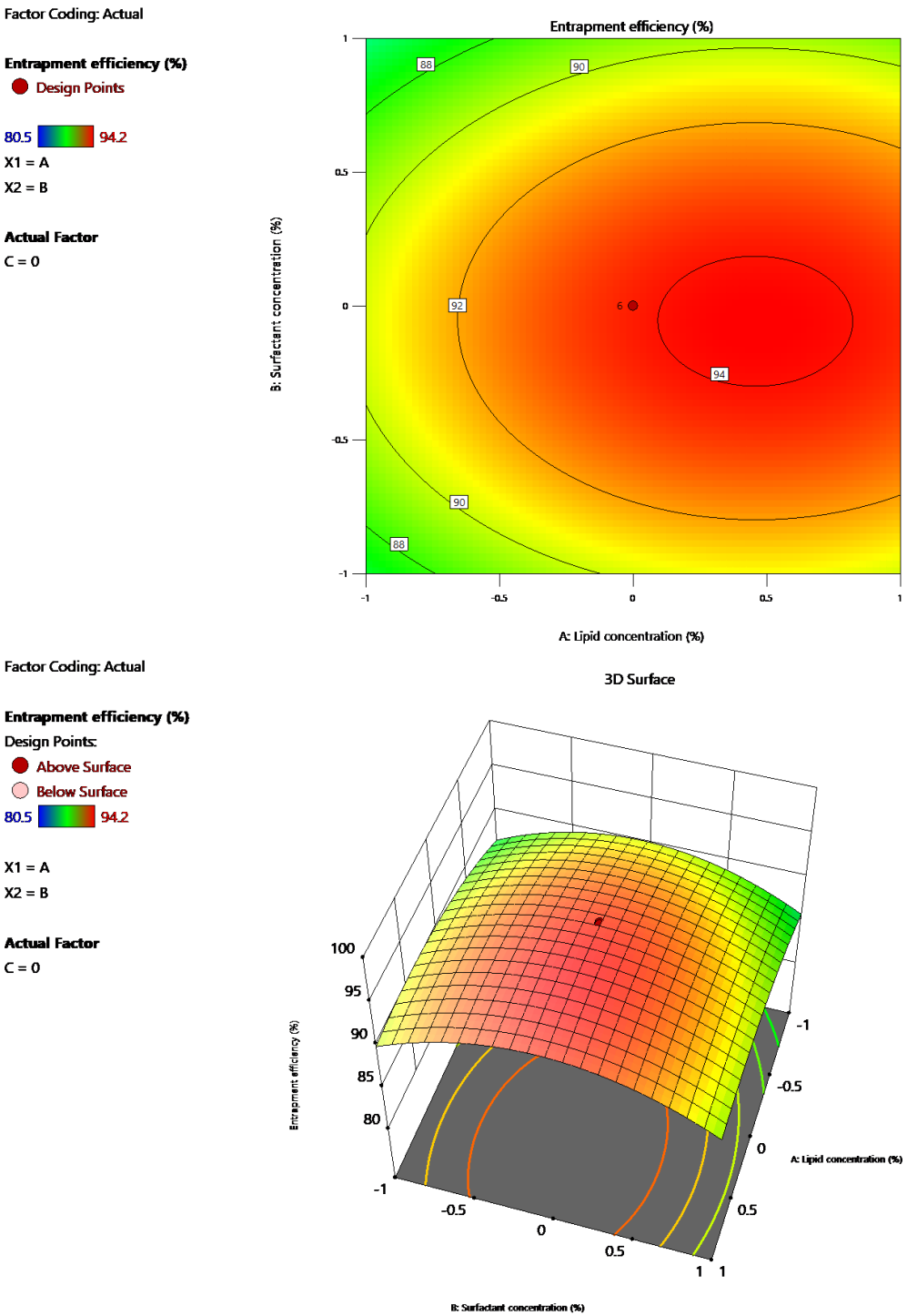


Figure 5: Contour Graphs and 3D Surface Graphs of Particle Size (nm) and Entrapment Efficiency (%).

is essential for consistent drug release and predictable *in vivo* behaviour.

Zeta potential values further supported the stability of the SLNs. The optimized formulation showed a zeta potential of -29.43±1.38 mV, which is close to the threshold required for electrostatic stabilization. Other formulations with lower magnitude values, such as -11.24±0.79 mV for RSLN-20, were more prone to aggregation. The negative surface charge likely arises from the lipid and phospholipid components, contributing to repulsive forces that maintain dispersion stability.

Entrapment Efficiency (EE) and Drug Loading (DL) exhibited a formulation-dependent trend. The highest EE was observed in RSLN-7 (94.2±1.03%), whereas the optimized formulation RSLN-12 showed a slightly lower EE of 82.6±1.79%. However, RSLN-12 demonstrated the highest drug loading of 7.86±0.23%, indicating more efficient utilization of lipid content. The contour

and 3D surface plots illustrate that both lipid and surfactant concentrations significantly influence EE, with an optimal region rather than a simple linear relationship.

The *in vitro* drug release profile showed that the optimized formulation achieved a sustained release of 78.6±1.6% over 24 hr. This controlled release behaviour contrasts with formulations having larger particle sizes and lower stability, which exhibited faster drug release. The sustained release can be attributed to the solid lipid matrix, which restricts drug diffusion and prolongs release duration. The anomalous transport mechanism (n=0.632) observed for RSLN-12 is characteristic of lipid nanoparticles where drug release is governed by both diffusion through the lipid matrix and matrix erosion. This dual mechanism is consistent with the high lipid crystallinity (confirmed by XRD) and the slow dissolution of the glyceryl behenate core, which together ensure sustained drug release over 24 hr. The lower n value for RSLN-12 compared to pure drug further confirms the sustained release nature of the formulation.

Morphological evaluation using SEM revealed that the nanoparticles were spherical and relatively uniform, with smooth surfaces and minimal aggregation. The absence of visible drug crystals suggests efficient encapsulation within the lipid matrix. XRD analysis further confirmed that repaglinide retained its crystalline nature, although with reduced peak intensity, indicating partial dispersion within the lipid structure.

While the optimized RSLN-12 showed acceptable six-month stability, the moderate PDI (0.319) and zeta potential (-29.43 mV) indicate room for improvement in long-term storage. Slight particle size increase (+9 nm) and reduced zeta potential (-1.2 mV) at 25ºC suggest gradual aggregation, consistent with reviewer concerns. To achieve a more robust system, we propose: (1) increasing Poloxamer 188 from 1.5% to 2.0%, (2) adding 0.2% phospholipid 90G, and (3) exploring Poloxamer 188:Tween 80 (1:1) combination. These modifications are predicted to achieve particle size <200 nm, PDI <0.25, and zeta potential <-35 mV for extended shelf-life.

The *in vivo* pharmacokinetic resultsdemonstrated significant improvement in drug performance. The optimized SLN formulation showed a lower C_{max} (276.4±21.2 ng/mL) compared to pure drug (348.6±28.3 ng/mL), indicating reduced peak-related side effects. The T_{max} was extended from 0.5±0.0 hr to 3.5±0.2 hr, confirming sustained drug release. Additionally, the half-life increased from 0.9±0.1 hr to 3.7±0.3 hr, and the AUC_{0-24} improved from 892.4±65.2 ng·h/mL to 1218.6±89.3 ng·hr /mL, indicating enhanced systemic exposure. The relative bioavailability also increased from 56.0±2.1% to 68.3±2.5%, suggesting improved absorption, possibly via lymphatic uptake. Alternative mechanisms that may contribute to the observed improvement include: (i) reduced enzymatic degradation of the drug within the gastrointestinal tract, (ii) increased intestinal permeability through transient tight junction opening, and (iii) inhibition of P-glycoprotein-mediated efflux by the lipid excipients.

Pharmacodynamic studies showed that the SLN formulation produced a more sustained reduction in blood glucose levels. For instance, at 4 hr, glucose levels were reduced to 152±14 mg/dL in the SLN group compared to 221±24 mg/dL for the pure drug group, with statistically significant differences (p<0.001). This sustained effect persisted up to 18 hr, demonstrating improved therapeutic performance.

Stability studies indicated that the optimized formulation remained stable over six months. At 25ºC, particle size increased slightly from 238.4±3.2 nm to 247.2±4.1 nm, while zeta potential decreased marginally from -29.4±1.1 mV to-28.2±1.4 mV. Entrapment efficiency decreased from 82.6±1.5% to 80.1±2.1%, and drug release increased slightly from 78.6±2.1% to 80.3±2.7%. Under refrigerated conditions (4ºC), these changes were minimal, confirming better stability at lower temperatures.

Finally, the study highlights that optimized SLNs with controlled particle size, adequate surface charge, and balanced composition can significantly enhance the pharmacokinetic and pharmacodynamic performance of repaglinide. The inclusion of results with standard deviation further strengthens the reliability and reproducibility of the findings, supporting the potential of SLNs as an effective drug delivery system for improved diabetes management.

CONCLUSION

In this study, we set out to tackle a real-world problem faced by many diabetic patients: the poor absorption and short action time of repaglinide, a drug that works well but fades too fast. By wrapping repaglinide inside tiny Solid Lipid Nanoparticles (SLNs), we aimed to give it a protective shell and a slower, more helpful release pattern.

The optimized formulation, RSLN-12, was tiny enough (around 238.4±12.4 nm) and stable enough (zeta potential near -29.43±1.38mV) to circulate effectively. It held a respectable amount of the drug and released it gradually over 24 hr unlike the pure drug, which dumps most of its content within hours. When tested in diabetic rats, the SLN version kept drug levels in the blood for much longer, extended the half-life nearly fourfold, and improved relative bioavailability by approximately 22% compared to the pure drug suspension possibly due to a combination of reduced first-pass metabolism and enhanced intestinal absorption. Just as importantly, it lowered blood sugar more steadily, avoiding the sharp peaks and crashes that can lead to hypoglycemia or poor glucose control. Future studies should focus on optimizing the surfactant-to-lipid ratio to achieve PDI < 0.25 and zeta potential < -35 mV for extended shelf-life stability.

Perhaps the most practical takeaway is this: the need for three daily doses of repaglinide could potentially be reduced to two, improving patient adherence and quality of life. The formulation also remained stable for six months under refrigeration, making it a realistic candidate for further development. In short, we've shown that a thoughtful, lipid-based nanocarrier can turn a challenging drug into a smarter, more patient-friendly therapy, offering hope for simpler, safer diabetes management in the future.

ACKNOWLEDGEMENT

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ABBREVIATIONS

SLN: Solid Lipid Nanoparticles; **PDI:** Polydispersity Index; **ZP:** Zeta Potential; **EE:** Entrapment Efficiency; **DL:** Drug Loading; **HPLC:** High-Performance Liquid Chromatography; **FTIR:** Fourier Transform Infrared Spectroscopy; **DSC:** Differential Scanning Calorimetry; **SEM:** Scanning Electron Microscopy; **XRD:** X-ray Diffraction; **ANOVA:** Analysis of Variance; **GOD-POD:** Glucose oxidase-peroxidase.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

AUTHOR CONTRIBUTIONS

Concept - Vedanshu Malviya; **Design** - Vedanshu Malviya, Shrikant Pande; **Supervision** - Shrikant Pande.; **Resources** - Vedanshu Malviya., Shrikant Pande.; **Materials** - Vedanshu Malviya., Shrikant Pande.; **Data Collection and/or Processing** - Vedanshu Malviya; **Analysis and/or Interpretation** - Vedanshu Malviya; **Literature Search** - Vedanshu Malviya.; **Writing** - Vedanshu Malviya.; **Critical Reviews** - Vedanshu Malviya, Shrikant Pande.

ETHICS APPROVAL

All animal experiments were conducted in accordance with CPCSEA guidelines, Government of India. The study protocol was approved by the Institutional Animal Ethics Committee (IAEC) (Approval No.: 1504//PO/RE/S/11/CPCSEA/17). All procedures were performed to minimize animal suffering.

PATIENT CONSENT

Not Required

SUMMARY

Repaglinide is effective in regulating blood sugar but has two major disadvantages: It is not easily soluble and most of it is degraded by the liver before it becomes effective. That is two or three times a day the patients should take it. In a bid to remedy this, the current research aims to develop encapsulation of the drug within small fat-like particles known as Solid Lipid Nanoparticles (SLNs).

We employed a basic hot-melt technique employing glyceryl behenate (the fat core), Poloxamer 188, and phospholipid 90G. The optimal batch (RSLN-12) was selected after testing 20 different batches and produced particles with a good and acceptable size, a stable surface charge, and good drug loading. The particles under the microscope appeared round.

In diabetic rats, the SLN version remained in the blood for a longer time than the plain drug. It increased its half-life of less than an hour to about 4 hr and an increased proportion of each dose got into the bloodstream. The blood sugar decreased in a more gradual fashion, without peaks and troughs. Six months storage also worked well with the formula.

In general, it makes repaglinide a slower, more consistent and predictable. This may result in reduced number of doses to patients each day and improved management of diabetes with reduced chances of sudden low blood sugar.

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