RESEARCH PAPER

Formulation and Characterization of Solid Lipid Nanoparticle Loaded with Selexipag as Model Drug

Mustafa Hamid Raheem [1] *, *Mazin Thamir Abdul- Hasan* [2]

[1] *Najaf Health Directorate, Najaf, Iraq*

[2] *Department of Pharmaceutics, Faculty of Pharmacy, University of Kufa, Najaf, Iraq*

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ABSTRACT

The objective of this study was to formulate and characterize selexipag-loaded solid lipid nanoparticles by using the ultrasound method, with four types of lipids (Palmitic acid, Stearic Acid, Glyceryl dibehenate, and Glyceryl Monostearate) evaluated for their impact on the solubility, the release behavior, and the potential improvement in oral bioavailability. Different variables like lipid concentration and lipid type used to optimize the formulation to achieve desired particle size along with maximum entrapment efficiency percentage and cumulative drug release percentage. The interaction between all the variables is well studied. Nineteen formulations of selexipag-loaded solid lipid nanoparticles were prepared and optimized by design of expert software version 13. The optimized formulation (made by 150mg of glyceryl monostearate, 90mg of poloxamer 407) showed the particle size 105±5 nm, the entrapment efficiency of 93% and the cumulative drug release percentage of 80.8% after 24hrs. The kinetic of release best fitted the first order kinetic model.

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INTRODUCTION

Solid lipid nanoparticles (SLNs) are colloidal particles of solid lipids that range in size from 10 to 1000 nm. These systems are capable for encapsulation of lipophilic or poorly water-soluble drug. Stabilizing SLNs with a layer composed of a single surfactant or a mixture of surfactants results in smaller particle sizes and improved storage stability [1,2]. Selexipag is an oral prostacyclin receptor agonist that acts by dilating pulmonary arteries and blocking smooth muscle cell proliferation. It is used in treatment of pulmonary arterial hypertension (PAH) to slow disease progression and lower the risk of hospitalization [3]. Based on the outcomes of the GRIPHON trial, the U.S. Food and Drug Administration (FDA) authorized selexipag in 2015 for the treatment of adult patients with pulmonary atrial hypertension [4]. Selexipag is classified as a class 2 drug by the Biopharmaceutics classification (BCS) indicated high permeability but poor water solubility, despite its clinical relevance, Selexipag exhibits very low aqueous solubility, which can limit its dissolution in the gastrointestinal tract and subsequently reduce its bioavailability. This physicochemical limitation presents a challenge for achieving consistent therapeutic effects and highlights the need for formulation strategies that can overcome poor solubility, making it a candidate for advanced

* *Corresponding Author Email: mustafahamid480@gmail.com*

drug delivery systems [5].

Several formulation strategies have been investigated to address the very low aqueous solubility and limited dissolution rate of Selexipag, including nanosuspensions, nanocrystals, liposomal carriers, and drug confinement in mesoporous silica.

Nanosuspension and nanocrystal approaches have continuously observed faster in-vitro dissolution and improved saturation solubility as compared to bulk Selexipag [5]. However, nanocrystals tend to cluster, amorphized, or undergo Oswald ripening because of their high surface energy, which compromises stability over time and there are manufacturing challenges including contamination risk and energy-intensive high-pressure homogenization. While nanosuspension drawbacks are physical instability, uniform dosing difficulty, and formulation complexity which required careful equilibrium of stabilizer, surfactant and solvents. Liposomal selexipag formulations have also been explored and show promise in improving intestinal permeability in ex-vivo [6], however Liposomes are costly high , have poor control over release, and are quickly removed unless PEGylated.

There is other formulation for selexipag which is selexipag formulation in liquisolid system but during the compression the liquid drug may be squeezed out lead to tablets with unsatisfactory hardness and effect drug release. Another solid formulation strategy is sublingual tablet of selexipag but the unpleasant taste of selexipag may make patients less likely to comply. Sublingual pills might provide little latitude in modifying dosage.

Despite these advances, systematic development of solid lipid nanoparticles (SLNs), Selexipag has not been formulated as SLNs before. This represents an important gap, as SLNs are a well-established delivery system capable of enhancing solubility, improving drug encapsulation, and modulating release.

The main benefits of solid lipid nanoparticles include controlled drug release, enhance solubility and bioavailability of poorly water-soluble drug, biocompatibility and physical stability during the storage. Their primary components provided the combined advantages of fat emulsions, liposomes, and polymeric nanoparticle systems while avoiding some of common drawbacks like burst release or scale up challenges. Since SLNs use physiological lipids rather than liposomes or polymeric nanoparticles, there is less chance of toxicity and regulatory approval is made easier. Any delivery system must be lipophilic (able to pass through lipid-based bio-membranes) and hydrophilic (able to dissolve in digestive fluids) to attain high oral bioavailability. As a targeted distribution system, SLNs are one of the few delivery systems that are interoperable, very stable, easily scalable, and adaptable [7]. Additionally, its solid lipid matrix improves drug protection and offers regulated release profiles that are advantageous for long-term illnesses like pulmonary hypertension. Therefore, the aim of this study is to develop and evaluate selexipag-loaded solid lipid nanoparticles (SLNs) prepared by the ultrasound method. Emphasis is placed on investigating how variables effect formulation characteristics. Particle size, entrapment efficiency, and loading capacity enhancement. Solubility enhancement and controlled release of the drug.

The goal is to optimize a formulation that can improve the oral delivery potential and therapeutic performance of selexipag. The new input and significance of current work introduce a novel approach by combining selexipag with a specific type of nanocarrier, potentially enhancing its therapeutic profile. While previous studies have focused on improving solubility and bioavailability, the current work may explore:

1) Targeted Delivery: directing selexipag to certain locations, like pulmonary arterial smooth muscle cells, using nanocarriers may improve medication effectiveness and lessen systemic side effects.

2) Controlled Release: creating nanocarriers that deliver selexipag over an extended period may enhance patient compliance and dosage regimens.

3) Combination Therapies: incorporating selexipag into multifunctional nanocarriers with other therapeutic agents could offer synergistic effects in treating pulmonary arterial hypertension. These advancements could represent a significant step forward in the development of more effective and patient-friendly treatments for pulmonary arterial hypertension.

MATERIALS AND METHODS

Materials

Selexipag and four types of lipids (Palmitic acid, stearic acid, glyceryl dibehenate, and glyceryl

monostearate) were supplied by hyperchem Ltd. in China. Surfactant poloxamer407 also was purchased from hyperchem Ltd. Amicon ultrafiltration tube Millipore 10KDa molecular weight cutoff sized 4ml supplied by Sigma Aldrich, and dialysis bag (molecular weight 14000, pore size 2.4nm) was supplied by Shanghai Dianrui biotechnology co., Ltd.

Experimental design of SLNs and statistical analysis

In this study, Design-Expert® software version13 was employed to optimize formulations of solid lipid nanoparticles (SLNs) loaded with selexipag, encompassed a total of 19 experimental runs included replicates at the center point to evaluate reproducibility. Response surface methodology RSM approach was employed using an optimal (custom) design with a unique numerical optimization technique was used. Formulation variables: lipid type and lipid concentration were used each at three levels (low, medium, and high). The sonication time was 10 minutes, and surfactant poloxamer407 was 90mg.

Key response parameters evaluated during optimization included loading capacity, entrapment efficiency, particle size, and polydispersity index. The optimization criteria were established to guarantee adequate drug release, minimize particle size, and maximize entrapment efficiency. The data were fitted to linear, two-factor interaction (2FI), and quadratic polynomial models. The best-fitting model for each response was selected based on the highest coefficient of determination (R^2), adjusted R^2, predicted R^2, and adequate precision values. Analysis of variance (ANOVA) was used to determine the statistical significance of each model and factor at a 95% confidence level ($p < 0.05$). Lack-of-fit was also assessed to confirm model adequacy. Regression equations were generated in both coded and actual forms to describe the relationship between the factors and the responses. Model diagnostics, including residual analysis and predicted vs. actual plots, were used to validate the adequacy of the fitted models.

Selexipag Solubility in Different Solid Lipids

Determining the solubility of the drug in various lipids was considered critically important, as it directly influences both the entrapment efficiency and the drug loading capacity [8]. To evaluate the solubilization potential of different lipid matrices, palmitic acid, stearic acid, glyceryl dibehenate, and glyceryl monostearate were individually tested for their ability to dissolve Selexipag. A precise amount of Selexipag dry powder (10 mg) was placed into a disposable glass test tube, followed by the gradual addition of molten lipid under continuous magnetic stirring. The process was carefully monitored to identify the minimum amount of lipid required to fully solubilize the drug. The final result is a clear pale-yellow lipid solution that was obtained with no visible undissolved drug particles, consistent with the experimental procedure done by Shah KA [9].

Preparation of Solid Lipid Nanoparticles

Ultrasonication was employed as the primary preparatory technique. A defined quantity of Selexipag was incorporated into the molten lipid, which had been heated to a temperature approximately 10 °C above its melting point. Simultaneously, distilled water containing the surfactant was heated to the same temperature. The lipid phase was then gradually introduced into the aqueous phase under constant magnetic stirring to form a coarse emulsion. This emulsion was subsequently subjected to sonication to produce a nano emulsion. Upon rapid cooling with cold water, solid lipid nanoparticles (SLNs) were formed, consistent with the method described by Pucek-Kaczmarek [10].

Characterization of SLNs Loaded with Selexipag
Particle Size Analysis

Particle size and polydispersity index (PDI) analyses were performed on the same day the solid lipid nanoparticle (SLN) formulations were prepared. To reduce viscosity and ensure accurate measurements, each formulation was diluted 1:30 in purified distilled water prior to measurement [11].The measurements were conducted using a nano laser particle size analyzer (Model ABT-9000, Angstrom Advanced Inc., USA), All the measurements were performed at temperature 25C and scattering angle of 90. The PH of dispersion was 6.5-7.0.

Entrapment Efficiency (EE%) and Loading Capacity (LC)

Solid lipid nanoparticles sample passed through a 0.45 µm nylon syringe filter to eliminate any unentrapped drug particles and ensure accurate quantification. The filtered sample then

centrifuged at 10,000 rpm for 30 minutes using Millipore Amicon tubes. After the centrifugation, the supernatant part was carefully separated from the pellet part. The pellet part that contained the entrapped drug was subsequently dissolved in methanol to get solution ready to be analyzed. For formulations that are prepared by glyceryl dibehenate, chloroform was used as the solvent to dissolve the pellet part and get solution to be analyzed, because the glyceryl dibehenate need nonpolar solvent to be dissolved. The resulting solutions (pellet+methanol) were analyzed using a UV–Visible spectrophotometer (Shimadzu, Japan) [12].

Entrapment efficiency and drug load calculated as:

$$\mathrm{LC} = \frac{\text{Amount of drug in SLNs}}{\text{Weight of SLNs}} \times 100 \quad (1)$$

$$\mathrm{EE\%} = \frac{\text{Amount of drug in SLNs}}{\text{Amount of initial drug}} \times 100 \quad (2)$$

X-Ray Diffraction (XRD)

The geometric scattering of radiation from crystal planes within a solid allows the presence or absence of the former to be determined the degree of crystallinity to be assessed of pure selexipag and solid lipid nanoparticle that loaded with selexipag by using Aeris XRD diffractometer (Malvern, Almelo, Netherland).

Morphology Study

Field emission scanning electron microscopy (FESEM) analysis of prepared SLN was done for morphological studies. Few drops of the dispersion were placed on glass slide and dried by air, then coated with gold in HUS-5 GB vacuum evaporator and observed in SEM at an acceleration voltage of 10 Kv to get high resolution images, the magnifications of 120.000X was performed [13].

In Vitro Drug Release

In vitro selexipag release from solid lipid nanoparticles (SLNs) prepared with different lipid matrices was evaluated using the dialysis bag diffusion method, as described by Hu et al. [14]. Each formulation was placed into a dialysis bag (molecular weight cut-off: 14,000 Da) that had been pre-soaked in phosphate-buffered saline (PBS, PH 6.8) for 12 hours. After sealing and clamping both ends, the dialysis bags were immersed in 100 mL of PBS containing 1% Brij to maintain sink conditions, and the setup was maintained under continuous magnetic stirring at 100 rpm and 37°C. At predetermined time intervals, 5 mL of the release medium was withdrawn and immediately replaced with an equal volume of fresh buffer to maintain constant volume and concentration gradient [15]. UV–Visible spectrophotometer (Shimadzu, Japan) was scanned the collected samples.

In addition to the intestinal-simulating release (PH 6.8), in vitro release of Selexipag from the solid lipid nanoparticles was also evaluated in simulated gastric fluid (SGF, pH 1.2) to mimic acidic condition, the process was the same for phosphate buffer PH 6.8 and acidic buffer PH 1.2.

RESULTS AND DISCUSSIONS

Optimization of SLNs Formulations

The Design-Expert® optimization employed four dependent responses: particle size (PS), polydispersity index (PDI), entrapment efficiency (EE%), and loading capacity (LC). These were chosen as they represent the critical quality attributes (CQAs) of solid lipid nanoparticles (SLNs) intended for oral delivery. Particle size and PDI determine uptake and uniformity, while EE% and LC reflect the drug incorporation efficiency and overall payload.

"Optimal" formulation was chosen; design-Expert® employed the desirability function to combine all four responses into a global score. The "optimal" formulation was selected because it maximized the composite desirability while meeting all predefined goals. The predicted optimum was validated experimentally, and the selected formulation showed a particle size of ~100 nm, PDI below 0.3, high entrapment efficiency, and a sustained release profile. The close agreement between predicted and observed values (≤5% error) confirmed the reliability of the optimization. According to numerical optimization criteria, the desired formulation was determined to comprise 150 mg of glyceryl monostearate (GMS), and 90 mg of Poloxamer 407. These criteria were designed to maximize entrapment efficiency while minimizing particle size and guaranteeing adequate drug release.

This formulation achieved a predicted entrapment efficiency of 93%, particle size of

105nm, loading capacity 5.8 and cumulative drug release of 80.8% at 24 hours. The optimization model indicated a high overall desirability score, supporting the selection of this combination for further evaluation.

The high entrapment efficiency can be attributed to the lipophilic nature of GMS, which provides a stable matrix for Selexipag incorporation. The small particle size suggested effective sonication and emulsification, enhancing cellular uptake and improving oral bioavailability. The observed release of 80% over 24 hours indicates sustained release behavior, which is advantageous for once-daily dosing.

These outcomes align with previous findings on GMS-based nanoparticles like [16], where smaller particle size and high drug-lipid affinity improved both encapsulation and release performance.

Selexipag Solubility in Lipids

Solubility of drug in the lipid matrix is the critical factor in the selection of the most suitable lipid for best solid lipid nanoparticles. Predicting lipid solubility is crucial first step in identifying the appropriate excipients to dissolve drug and ensure efficient drug loading and stability of solid lipid nanoparticle formulations [17]. In this study, Selexipag exhibited the highest solubility in glyceryl monostearate (GMS), making it the most promising lipid candidate for SLN development. In contrast significantly low solubility was observed in other lipids such as stearic acid, palmitic acid, and glyceryl dibehenate, see (Table 1).

This result may be explained by GMS's amphiphilic character, which may improve its ability to dissolve drugs that are not very soluble in water, such as Selexipag. GMS's dual hydrophilic (hydroxyl) and lipophilic (fatty acid chain) domains made it easier for the drug molecules to engage with it. A similar trend was reported by Kumar R. who found that lipid-based solubility screening through stepwise heating and stirring is an effective technique for identifying suitable lipids for nanoparticle formulation [18]. In our case, 10 mg of Selexipag was gradually mixed with increasing amounts of lipid under magnetic stirring and gentle heating until complete visual dissolution of the drug in the lipid matrix was achieved.

These solubility results affect the final SLN formulations' stability, drug release profile, and entrapment efficiency in addition to directing lipid selection. It is anticipated that Selexipag better solubilization in GMS will increase drug loading capacity and boost formulation performance.

Preparation of Solid Lipid Nanoparticles

Several factors and process-related factors influenced the synthesis of solid lipid nanoparticles by using ultrasonication method in this study. The variables included the physicochemical characteristics of the lipid, the concentration of the lipid matrix, and the lipid type. These parameters play a crucial role in determining particle size, entrapment efficiency, and dispersion stability see (Table 2).

Apart from formulation parameters, SLN formation was also greatly impacted by processing conditions like elevated temperature during emulsification, suitable degree of temperatures help maintain the lipid in a molten state, allowing better dispersion into the aqueous phase. For this reason, optimizing both formulation and processing variables is crucial to achieving stable, nanosized particles with effective drug loading [19].

Effect of Formulation Variables

Lipid Concentration

The particle size of the SLN formulations was found to be significantly influenced by the lipid amount in this study; there was a noticeable

Table 1. Solubility of Selexipag in Different Lipids.

Lipid	Solubility (mg of selexipag per 1000mg of lipid)
Palmitic Acid	16.6 mg
Stearic Acid	20 mg
Glyceryl Dibehenate	16.39 mg
Glyceryl Monostearate	83.3 mg

Table 2. SLNs Loaded with Selexipag and Their Response Parameters.

Run	Lipid concentration (mg)	Lipid type	Particle size (nm)	Poly dispersity (PDI)	Entrapment efficiency (EE%)	Loading capacity (LC)
1	150	palmitic acid	224	0.01	24.84	1.55
2	300	glyceryl monostearate	389	0.023	97.91	3.158
3	300	glyceryl dibehenate	656	0.015	48.47	1.563
4	225	glyceryl monostearate	382	0.01	94.84	4.03
5	150	stearic acid	212	0.012	29.66	1.853
6	150	glyceryl dibehenate	352	0.013	23.9	1.493
7	150	glyceryl monostearate	94.3	0.096	93.73	5.58
8	150	glyceryl monostearate	74.9	0.095	93.73	5.58
9	300	glyceryl monostearate	406	0.009	97.91	3.158
10	300	stearic acid	270	0.01	59.18	1.9
11	225	palmitic acid	262	0.013	37.81	1.6
12	225	glyceryl dibehenate	431	0.013	35.26	1.5
13	225	palmitic acid	263	0.01	37.81	1.6
14	300	stearic acid	281	0.01	59.76	1.9
15	225	glyceryl dibehenate	447	0.013	35.26	1.5
16	150	glyceryl monostearate	86	0.234	93.73	5.85
17	300	palmitic acid	299	0.011	50.06	1.614
18	225	stearic acid	268	0.008	44.22	1.88
19	225	stearic acid	262	0.013	44.22	1.88

increase in particle size when the lipid content was increased from 150 mg to 300 mg because the lipid phase is more viscous at higher amounts, which can prevent efficient size reduction during ultrasonication and result in larger particle formation. This observation is consistent with prior findings like Aditya NP et al. who noted that elevated lipid amounts tend to increase the viscosity of the system, thereby limiting the efficiency of energy transfer during emulsification and resulting in larger particle sizes [20]. In addition to the amount, the chemical nature and crystallinity of lipids also played a critical role. Lipids that form highly crystalline structures with an orderly lattice tend to expel the drug during the solidification process, thereby reducing drug entrapment. In contrast, more complex lipids (such as those containing a mixture of mono-, di-, and triglycerides) form less perfect crystalline matrices. These matrices contain structural imperfections that create spaces, or "drug pockets" allowing for better drug accommodation [21].

The results observed in our formulations align with this concept: lipids with a more disordered or heterogeneous structure, such as glyceryl monostearate (GMS), allowed for better drug incorporation and smaller particle sizes compared to more crystalline lipids like glyceryl dibehenate, this finding is in agreement with earlier reports done by (Jenning V. and Gohla SH.) and Wissing SA. et al., who demonstrated that lipids with lower crystallinity and higher structural disorder favor smaller particle sizes and improved drug entrapment due to the presence of imperfections within the lipid matrix [22,23].

Lipid Type

The type of lipid played a significant role in determining the particle size. Fatty acids such as palmitic acid and stearic acid, which have relatively shorter carbon chains, were associated with smaller particle sizes and this with agreement with previous studies [24]. This is likely due to and simpler molecular structure, which facilitates the formation of finer emulsions during ultrasonication. In contrast, more complex lipids such as glyceryl monostearate and glyceryl dibehenate produced relatively larger particles, possibly due to their higher molecular weight and longer chain structures, see (Fig. 1).

These results collectively suggest that glyceryl monostearate is the most suitable lipid among those tested for the formulation of Selexipag-loaded SLNs, offering optimal particle size, drug encapsulation, and loading capacity.

Particle size increases in the following order: (glyceryl dibehenate > Glyceryl monostearate >stearic acid>palmitic acid).

Characterization of SLNs Loaded with Selexipag
Particle Size Analysis

The particle size of the solid lipid nanoparticles (SLNs) was markedly influenced by multiple parameters, including the type of lipid, and

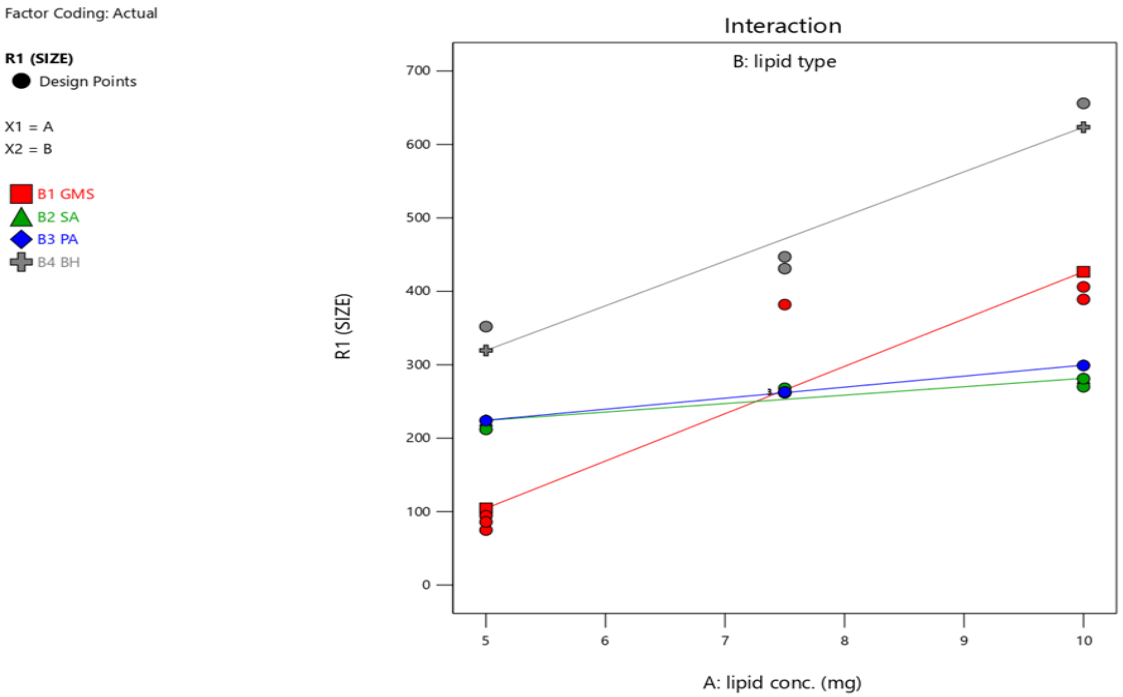

Fig. 1. Effect of the Lipid type and Concentration on Particle Size. (GMS: Glyceryl Monostearate, SA: Stearic a\Acid, PA: Palmitic Acid, BH: Glyceryl Dibehenate).

lipid concentration. The energy input during ultrasonication plays a critical role in particle formation by facilitating droplet disruption and nanoparticle generation through cavitation forces and this reported by Emami J et al. [25]. At higher lipid concentrations, the likelihood of drug molecules becoming entrapped within or adsorbed onto lipid particles increases. This interaction contributes to the formation of denser lipid matrices that require greater energy for size reduction, ultimately leading to larger particle sizes [26]. These findings are consistent with previous studies indicating that both drug incorporation and lipid physicochemical properties can critically impact the nanostructure and size distribution of SLNs. Mukherjee S. et al. and Beloqui A et al., they highlight the importance of optimized formulation parameters in achieving desirable nanoparticle characteristics [27,28].

Entrapment Efficiency (EE%) and Loading Capacity (LC)

Entrapment efficiency and loading capacity were closely related to the solubility of Selexipag in each lipid. Glyceryl monostearate GMS, which showed the highest solubility for Selexipag, resulted in the highest %EE and LC across all three tested concentrations (150 mg, 225 mg, and 300 mg). This observation is in agreement with previous findings, which reported that greater drug solubility in the lipid phase enhances entrapment efficiency by promoting better distribution of the drug within the lipid matrix [29].

Glyceryl monostearate (GMS) exhibited the highest entrapment efficiency (EE%) and loading capacity (LC), which can be attributed to two key factors: the relatively high solubility of Selexipag in GMS and its long carbon side chain, which enhances drug incorporation within the lipid matrix.

In contrast, palmitic acid and stearic acid demonstrated the lowest EE% and LC values. This outcome is likely due to their shorter carbon chains and limited ability to solubilize Selexipag, as confirmed by preliminary solubility studies, see (Fig. 2).

Glyceryl dibehenate also exhibited relatively low entrapment efficiency and drug loading capacity, despite it possessing a long carbon chain (C-22), this outcome is primarily attributed

to its highly crystalline and structurally ordered nature, which limits the ability of this lipid matrix to accommodate drug molecules. The rigid lattice structure restricts molecular mobility and reduces the free volume available for drug entrapment. These findings are consistent with previous reports by Hou D, Xie C, Huang K, Zhu C that demonstrated that lipids with a high degree of crystallinity tend to encapsulate drugs less efficiently due to limited imperfections in their solid-state structure that could otherwise serve as drug-binding sites [30].

The cumulative drug release from the optimized GMS-based SLN formulation reached 80.8% after 24 hours, indicating sustained release behavior and efficient drug diffusion from the nanoparticle system under the tested conditions.

Morphology Study

Field emission scanning electron microscopy (FESEM) analysis was carried out to examine the surface morphology and particle size of the optimized Selexipag-loaded SLNs. As shown in (Fig. 3), the nanoparticles exhibited predominantly spherical to near-spherical morphology with relatively smooth surface characteristics and no evidence of structural irregularities. The particle size observed directly from the micrograph ranged between approximately 68–104 nm, which is in good agreement with the nanoscale dimensions obtained from the formulation. The consistent distribution of sizes and shapes suggests that Selexipag-loaded SLNs were successfully fabricated with favorable physicochemical characteristics, hence bolstering their appropriateness for other pharmacological uses. The micrograph showed only slight aggregation in some areas, which is usually ascribed to the drying and sample preparation procedure rather than the inherent instability of the nanoparticles. Overall, the nanoscale morphology of the SLNs was maintained, remaining distinct and evenly distributed, this is consistent with previous observations in SLNs [21].

X-Ray Diffraction (XRD)

A useful technique helps in characterizing the crystalline nature of the compound and determine the polymorphic shifts present. X-ray diffraction (XRD) plays a prominent role because they can provide structural information on the dispersed particles [31].

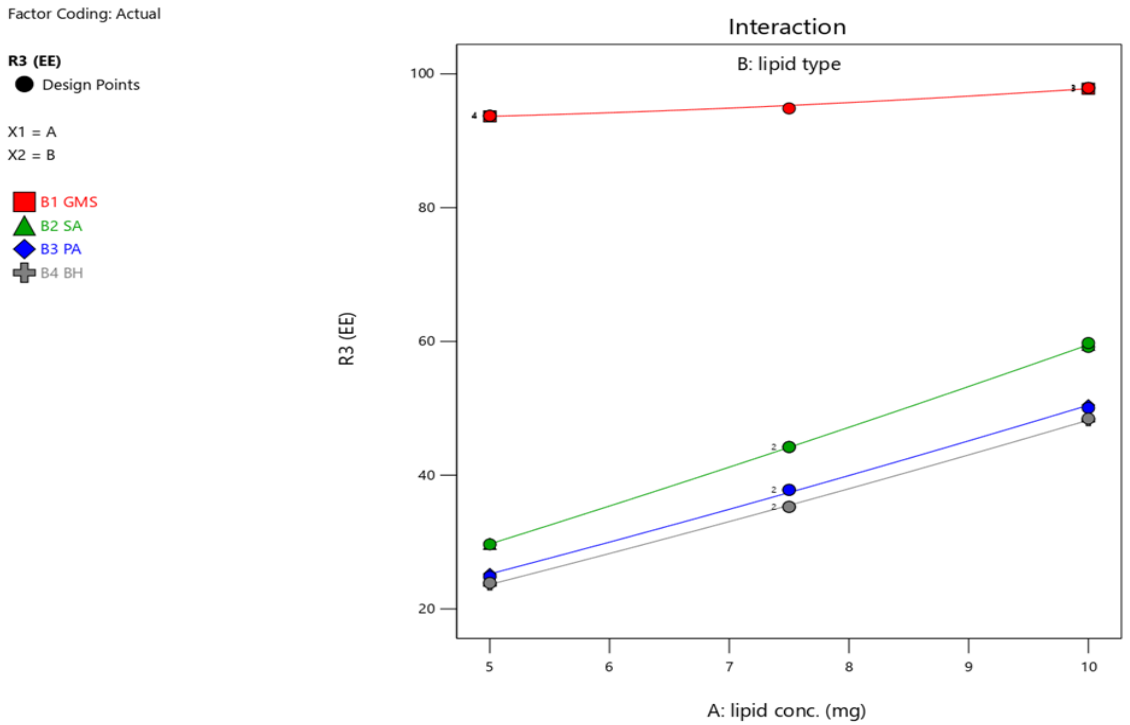

Fig. 2. Effect the Lipid type and Concentration on Entrapment Efficiency EE% (GMS: Glyceryl Monostearate, SA: Stearic Acid, PA: Palmitic Acid, BH: Glyceryl Dibehenate).

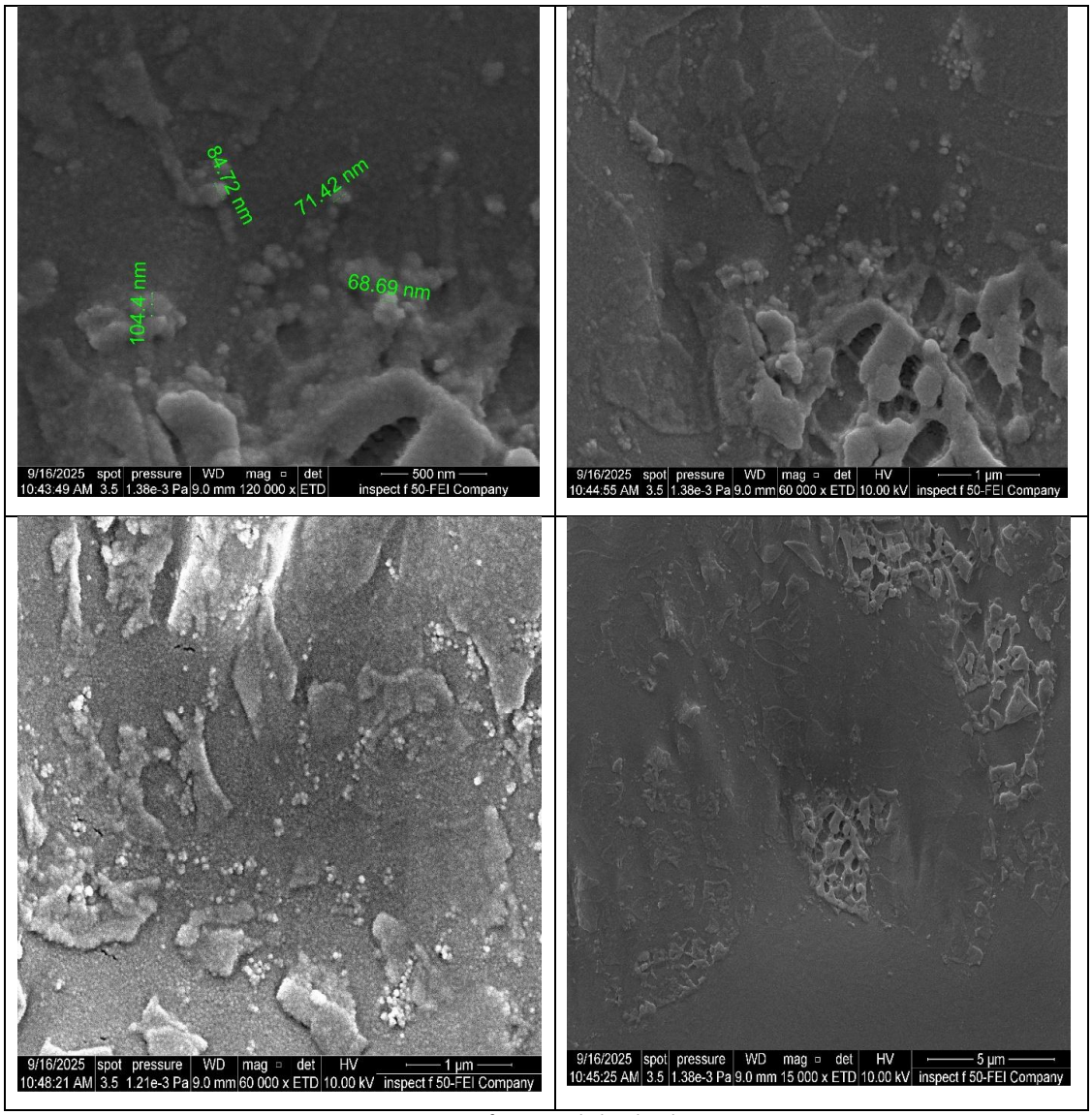

Fig. 3. FESEM of SLNs Loaded with Selexipag.

Pure Selexipag XRD pattern showed several strong diffraction peaks, which are indicative of a crystalline solid and point to long-range structural order (see Fig. 4). The optimized SLN formulation, on the other hand, demonstrated a significant reduction in drug crystallinity and partial conversion to an amorphous or highly dispersed state within the lipid matrix, as seen in (Fig. 5), along with a noticeable attenuation and broadening of these distinctive peaks (and in some areas, an almost total disappearance). Smaller crystallite domains and/or enhanced structural disorder following formulation in SLNs are indicated by the decrease in diffraction intensity and the increase in peak broadening, which perhaps helps explain the drug's better dissolving behavior. Residual low-intensity peaks in the SLN trace signify partial loss of crystallinity for a fraction of the drug [32].

In vitro Drug Release

An initial burst release of Selexipag was observed in SLNs prepared with palmitic acid and stearic acid, followed by a slower release phase. This behavior is attributed to the poor solubility of Selexipag in these lipids, which led to a significant portion of the drug being localized near the surface

of the nanoparticles. Specifically, formulations with palmitic acid exhibited a pronounced burst release beginning near 40%, rising rapidly to approximately 70% within the first 5 hours. Similarly, stearic acid-based SLNs demonstrated a burst release of around 30%, increasing to ~60% in the same period.

Although the solubility of Selexipag in glyceryl dibehenate was also low, its release from this matrix was more sustained, this is explained by the highly crystalline and rigid structure of glyceryl dibehenate, which consists of long C-22 behenic acid chains, its dense and ordered structure reduces porosity and drug mobility, forming a strong diffusion barrier that slows down drug release. These results are consistent with previous findings, where long-chain, crystalline lipids were shown to retard drug diffusion due to limited molecular mobility [33].

In contrast, SLNs formulated with glyceryl

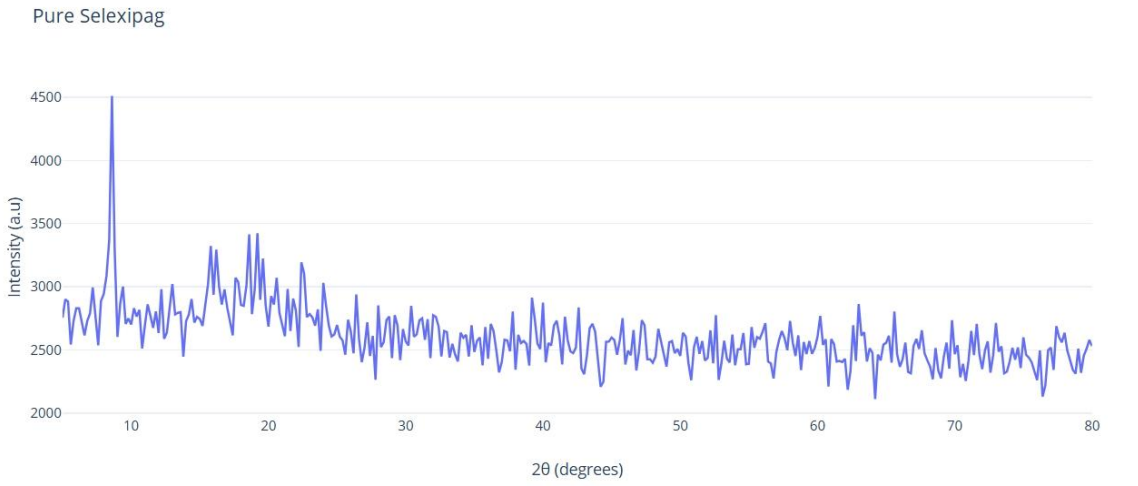

Fig. 4. XRD Pattern of Pure Selexipag Powder.

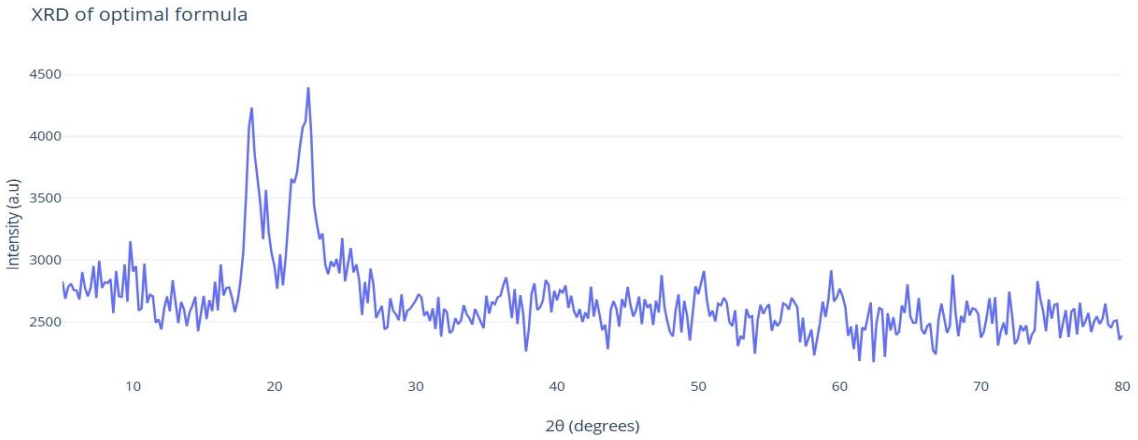

Fig. 5. XRD Pattern of the Optimal Formula of SLNs Loaded with Selexipag.

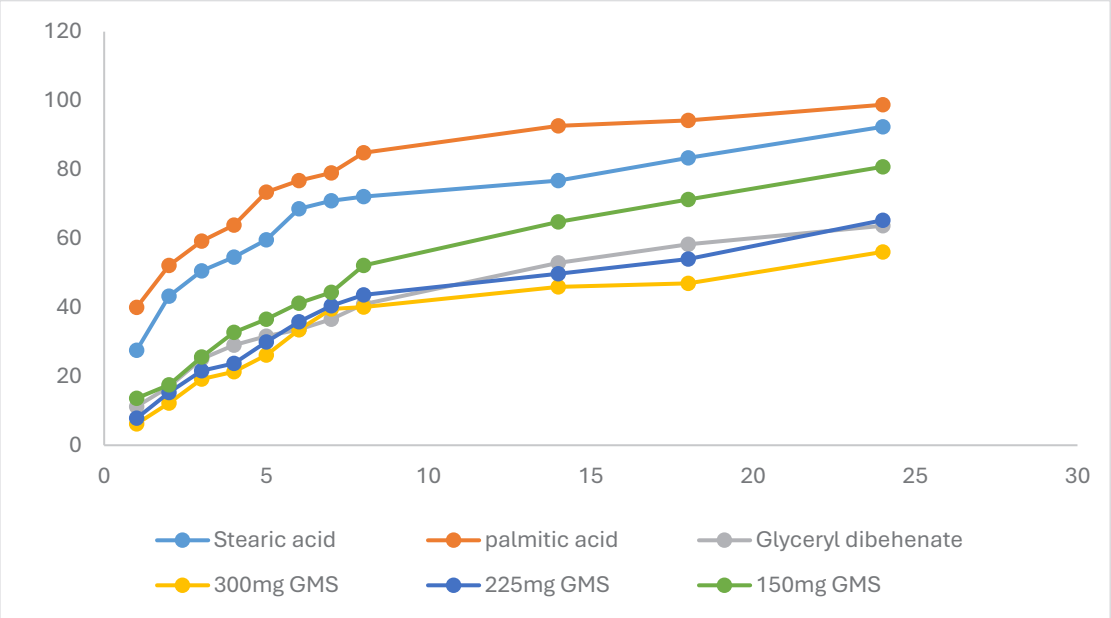

Fig. 6. In Vitro Release of Different Formulations of SLNs Loaded with Selexipag in PH 6.8 Buffer Solution.

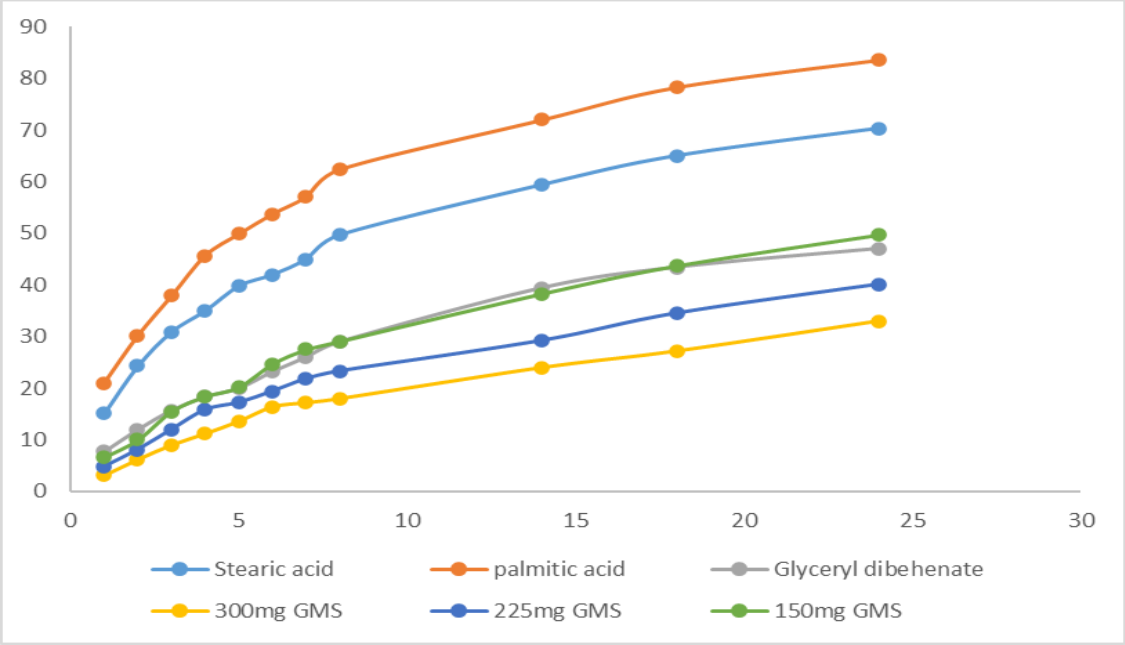

Fig. 7. In Vitro Release of Different Formulations of SLNs Loaded with Selexipag in Acidic Buffer PH 1.2.

monostearate (GMS) exhibited controlled and prolonged drug release. This is likely due to the higher solubility of Selexipag in GMS, which facilitated deeper incorporation into the lipid matrix. Moreover, increasing the concentration of GMS in the formulation further extended the release duration, as the drug became more strongly embedded within the matrix.

Among the tested formulations, the one containing 150 mg GMS showed the most desirable

release profile, which best fits a first-order kinetic model, indicating concentration-dependent drug release over time, see (Fig. 6).

Selexipag exhibit low solubility in acidic media, this characteristic is similar to other lipophilic drug formulated in SLNs, where the release rate can be affected by solubility in the dissolution medium [5].

In comparison with phosphate buffer pH 6.8, the release of selexipag from SLNs in acidic media buffer (pH 1.2) was often slower. The decreased solubility of Selexipag in acidic media and possible interactions between the lipid matrix and acidic ions could be the cause of this delayed release, see (Fig. 7). Formulations containing glyceryl monostearate showed minimal burst release in both media, indicating strong drug–lipid interactions and sustained release properties [34]. These results suggest that SLNs could protect Selexipag from rapid dissolution in the stomach, potentially improving oral bioavailability and providing controlled release in the intestine.

CONCLUSION

Solid lipid nano particle is suitable carrier system for incorporation of selexipag. Selexipag is poorly water-soluble drug that was effectively encapsulated into nanoparticles produced by ultrasound method and stabilized by surfactant poloxamer407. Glyceryl monostearate GMS provided reasonable solubility capacity for selexipag. Many variables showed a huge impact on SLNs production and characterization.

The desired formulation showed desirable particle size and the drug release showed sustained prolonged release from SLNs and followed first order kinetic model. Entrapment efficiency was maximized and that's improved the absorption and bioavailability.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this manuscript.

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