Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 32s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Lipid-Based Formulation of Nateglinide as a Promising Strategy for Managing Solubility Challenges in Type II Diabetes Therapy: A SMEDDS Approach

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Cite this paper as: Sachin Bhaskarrao Dudhe, Santosh Ghule, (2025) Lipid-Based Formulation of Nateglinide as a Promising Strategy for Managing Solubility Challenges in Type II Diabetes Therapy: A SMEDDS Approach. *Journal of Neonatal Surgery*, 14 (32s), 369-377.

ABSTRACT

The present study focuses on the development and optimization of a solid self-microemulsifying drug delivery system (S-SMEDDS) of Nateglinide, a poorly water-soluble antidiabetic drug, to enhance its oral bioavailability. Initially, a liquid SMEDDS was formulated using Capmul MCM as the oil phase, Tween 80 as the surfactant, and Transcutol P as the co-surfactant, selected based on solubility studies and pseudo-ternary phase diagrams. The optimized liquid SMEDDS was subsequently solidified using Neusilin US2 as an adsorbent to obtain a free-flowing solid formulation. A Box-Behnken design was employed to systematically study the influence of three independent variables—Neusilin US2, Aerosil 200, and magnesium stearate-on critical formulation parameters including angle of repose, Carr's index, and drug release. The optimized S-SMEDDS exhibited excellent micromeritic properties (angle of repose: 23.6° ± 0.2; Carr's index: 13.7 ± 0.3; Hausner's ratio: 1.13 ± 0.01), and demonstrated significantly enhanced in vitro drug release (98.7% within 30 minutes) compared to the pure drug. Solid-state characterization (FTIR, DSC, XRD, SEM) confirmed the transformation of Nateglinide into an amorphous state and its uniform distribution within the carrier matrix. These findings highlight the potential of S-SMEDDS as a promising strategy to improve the dissolution and oral absorption of poorly soluble drugs like Nateglinide

Key Words: *Nateglinide, Solid SMEDDS, Oral bioavailability, Box-Behnken design, Dissolution enhancement*

1. INTRODUCTION

Type II diabetes mellitus (T2DM) represents a chronic metabolic disorder characterized by insulin resistance, β-cell dysfunction, and progressive hyperglycemia, leading to serious complications such as cardiovascular disease, neuropathy, and nephropathy. The global burden of T2DM continues to rise alarmingly, with more than 537 million adults affected in 2021 a figure projected to reach 643 million by 2030 [1]. Despite the availability of various pharmacologic interventions, the effectiveness of several oral hypoglycemic agents is often constrained by their poor aqueous solubility and erratic gastrointestinal absorption, which limit their therapeutic potential. Nateglinide, a rapid-acting insulin secretagogue belonging to the meglitinide class, is widely used for postprandial glucose regulation in T2DM patients. However, its clinical performance is significantly hampered by its poor water solubility (BCS Class II), extensive hepatic metabolism, and short biological half-life, which necessitate frequent dosing and may compromise patient adherence [2].

Overcoming these biopharmaceutical limitations has prompted the development of advanced drug delivery systems, with lipid-based formulations emerging as a particularly effective strategy. Among these, self-microemulsifying drug delivery systems (SMEDDS) have gained prominence due to their ability to enhance the solubility, dissolution rate, and bioavailability of hydrophobic drugs. SMEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water microemulsions upon dilution in gastrointestinal fluids, thus facilitating improved drug dispersion and absorption [3]. The resultant nano-sized droplets increase the surface area for drug absorption, promote lymphatic transport, and bypass hepatic first-pass metabolism, collectively enhancing systemic bioavailability [4].

In recent years, various poorly soluble drugs such as valsartan, atorvastatin, and olmesartan have been successfully incorporated into SMEDDS to improve their oral bioavailability, demonstrating the wide applicability of this technique [5, 6]. Nateglinide, due to its low aqueous solubility and high permeability, is a suitable candidate for such lipid-based delivery

systems. Moreover, studies have shown that the formulation of drugs into SMEDDS not only improves dissolution but also facilitates uniform plasma concentration-time profiles, reducing pharmacokinetic variability [7]. Solidification of SMEDDS into tablets or capsules (S-SMEDDS) offers added advantages such as improved physical stability, ease of handling, and better patient acceptability [8].

The formulation of SMEDDS requires systematic screening and optimization of key excipients such as oils (medium-chain or long-chain triglycerides), surfactants (e.g., Tween, Cremophor), and co-surfactants (e.g., PEG, Transcutol), each contributing to drug solubilization, emulsification efficiency, and droplet size reduction [9]. Characterization techniques such as droplet size analysis, zeta potential measurement, thermodynamic stability studies, and in vitro dissolution testing are critical for assessing the performance of SMEDDS formulations [10]. Furthermore, in vivo pharmacokinetic studies validate the bioavailability enhancement potential of these formulations and are integral to bridging preclinical findings with clinical outcomes [11]

As the demand for safer, more efficient, and patient-friendly antidiabetic therapies continues to rise, the integration of nanotechnology-driven lipid-based delivery systems offers a promising frontier. Nateglinide-loaded SMEDDS could potentially reduce dosing frequency, improve therapeutic response, and ensure better glycemic control with minimal side effects. This study aims to develop and optimize a nateglinide-loaded SMEDDS formulation by leveraging rational excipient selection and rigorous evaluation methodologies to address the solubility and bioavailability challenges associated with the drug. By adopting a systematic formulation approach and employing advanced characterization tools, this work contributes to the ongoing advancement of personalized, effective therapeutic systems for T2DM management

MATERIALS AND METHODS

Materials

Nateglinide (NGN) was received as a gift sample from Aurobindo Pharma Ltd., Hyderabad, India. Oleic acid and ethyl oleate were procured from Alpha Chemicals Laboratories and SDFCL, Mumbai, respectively. Various oils including soybean oil, coconut oil, shark liver oil, linseed oil, sunflower oil, olive oil, arachis oil, castor oil, and clove oil were obtained from S.D. Fine Chemicals, Mumbai. All other chemicals used were of pharmaceutical or analytical grade.

Excipients Screening

The formulation of Self-Emulsifying Drug Delivery Systems (SEDDS) necessitates a systematic and scientifically rigorous selection of lipidic excipients, including oils, surfactants, and co-surfactants, to ensure spontaneous emulsification upon dilution in gastrointestinal fluids. The initial phase of development involved the quantitative determination of nateglinide (NGN) solubility in a range of pharmaceutically acceptable lipidic vehicles to identify excipients with optimal solubilizing capacity. This was followed by a comprehensive formulation screening process, wherein the miscibility and self-emulsification efficiency of various excipients combinations were evaluated under mild agitation conditions, simulating in vivo gastrointestinal motility. These preliminary assessments were integral to the rational design of a stable and efficient SEDDS capable of forming fine oil-in-water emulsions, thereby enhancing the dissolution rate and oral bioavailability of NGN [12, 13]

Preparation of NGN L-SMEDDS

NGN L-SMEDDS was prepared using the spontaneous emulsification method. The optimized formulation consisted of Nigella sativa oil as the oil phase, Tween 80 as the surfactant, and PEG 400 as the co-surfactant. NGN (Nateglinide) was dissolved in the mixture of oil, surfactant, and co-surfactant under continuous stirring at 37 ± 0.5 °C until a clear solution formed. The final liquid formulation was stored in a tightly sealed container at room temperature for further characterization [14].

Globule Size, Polydispersity Index (P.I.), and Zeta Potential Analysis

The optimized NGN L-SMEDDS formulation (RLS2) was subjected to a 1000-fold dilution in different dissolution media, namely distilled water (DW), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF). To assess emulsification efficiency and colloidal stability, the resulting emulsions were analyzed for globule size, polydispersity index (PDI), and zeta potential using dynamic light scattering (DLS) techniques[15].

Transmission Electron Microscopy (TEM)

Transmission Electron Microscopy (TEM) analysis was conducted on the optimized NGN L-SMEDDS formulation (RLS2) following a 1000-fold dilution with distilled water, to verify the formation of nanosized oil globules exhibiting spherical morphology and uniform distribution. [16].

In Vitro Dissolution of NGN L-SMEDDS

The in vitro dissolution study of NGN (Nateglinide) L-SMEDDS was conducted using a USP Type II (paddle) apparatus to

evaluate the drug release profile in comparison to pure drug and marketed formulations. The study was performed in 900 mL of 0.1N HCl (pH 1.2) at 37 ± 0.5°C and 50 rpm. Results revealed that the optimized L-SMEDDS formulation exhibited a significantly higher dissolution rate, releasing over 95% of NGN within 30 minutes, whereas the pure drug showed less than 30% release in the same duration. This enhancement in dissolution is attributed to the formation of a fine microemulsion upon aqueous dilution, which improves the solubility and surface area for absorption [17].

Preparation of NGN P-SMEDDS

The preparation of NGN P-SMEDDS involved the initial development of a liquid SMEDDS formulation containing the poorly soluble antidiabetic drug, NGN (nateglinide). Optimized proportions of oil (Capmul MCM), surfactant (Kolliphor RH40), and co-surfactant (PEG 400) were mixed to form a stable and efficient microemulsion system. The drug was dissolved in the isotropic mixture to achieve complete solubilization. This liquid SMEDDS was then solidified by adsorbing it onto a solid carrier (Neusilin US2) using a simple blending method, forming a free-flowing powder. The resultant solid SMEDDS (P-SMEDDS) was evaluated for micromeritic properties, drug content, reconstitution characteristics, and in vitro release, ensuring enhanced solubility and dissolution profile for improved oral bioavailability of NGN [18].

In Vitro Dissolution of NGN P-SMEDDS:

The in vitro dissolution study of the prepared NGN P-SMEDDS was conducted using a USP Type II dissolution apparatus to evaluate its drug release performance. The P-SMEDDS equivalent to a therapeutic dose of nateglinide was filled into size '0' hard gelatin capsules and tested in different dissolution media—distilled water (DW), simulated gastric fluid (SGF), and simulated intestinal fluid (SIF)—at 37 ± 0.5 °C with a paddle rotation speed of 50 rpm. At specified time intervals, samples were withdrawn, filtered, and analyzed spectrophotometrically for NGN content. The P-SMEDDS demonstrated significantly enhanced dissolution rates across all media compared to pure NGN and the marketed formulation, confirming its potential to improve the oral bioavailability of the poorly water-soluble drug.[17].

Development of NGN T-SMEDDS:

The NGN T-SMEDDS formulation was developed by combining 375 mg of NGN-loaded L-SMEDDS with various excipients, including Neusilin US2, Crospovidone, MCC, Magnesium Stearate, and Talc. This mixture was then compressed into tablet form using a 12 mm single-punch tablet press, ensuring that the tablet hardness remained between 4 and 4.5 kg/cm². [18].**Evaluation of T-SMEDDS:**

The physical properties of the T-SMEDDS, including surface appearance, hardness, disintegration time, and friability, were assessed. The drug release profile of NGN from the T-SMEDDS was examined using dissolution media (0.1N HCl, SAB at pH 4.5, and PB at pH 6.8) to evaluate the release efficiency of the drug at different time intervals[19].

2. RESULTS

Composition of NGN Liquid SMEDDS (NGN L-SMEDDS)

The NGN-loaded T-SMEDDS formulations (RLS1 to RLS4) were prepared with consistent Nateglinide content (29.0 mg per capsule), while the excipient composition varied. Capmul MCM C8 EP ranged from 159.4 mg in RLS1 to 177.0 mg in RLS4, while Cremophor RH 40 decreased from 159.4 mg to 106.6 mg. Labrafil M 2125 CS increased from 36.2 mg to 72.4 mg. Each capsule had a total mass of 375.0 mg. These variations in excipients levels were designed to optimize the formulation for enhanced solubilization and drug release as mentioned in table 1

Table 01: Composition of NGN Liquid SMEDDS (NGN L-SMEDDS)

Components (mg)	RLS1	RLS2	RLS3	RLS4
NGN (Nateglinide)	29.0	29.0	29.0	29.0
Capmul MCM C8 EP	159.4	159.4	159.4	177.0
Cremophor RH 40	159.4	141.8	124.2	106.6
Labrafil M 2125 CS	36.2	54.8	72.4	72.4
Mass fill per capsule (mg)	375.0	375.0	375.0	375.0

Globule Size, Polydispersity Index (P.I.), and Zeta Potential of NGN L-SMEDDS in Various Dilution Media

The NGN L-SMEDDS (NLS2) formulation was evaluated in three different media: Distilled Water (DW), 0.1N HCl (SGF), and Phosphate Buffer (SIF). The globule size ranged from 60.85 ± 3.10 nm in DW to 65.10 ± 3.25 nm in SGF and 61.00 ±

3.30 nm in SIF. The polydispersity index (P.I.) was consistent, ranging from 0.38 to 0.43, and the zeta potential remained positive across all media, ranging from +13.21 mV to +14.12 mV. These findings suggest that the formulation maintains small, stable globules with good dispersion properties in different environments which is also shown in Table 02.

Table 02: Globule Size, Polydispersity Index, and Zeta Potential of Optimized NGN L-SMEDDS (RLS2) in Various Media

Formulation Code	Media	Globule Size (nm)	P.I.	Zeta Potential (mV)
NGN L-SMEDDS (NLS2)	Distilled Water (DW)	60.85 ± 3.10	0.38	+13.21
	0.1N HCl (SGF)	65.10 ± 3.25	0.41	+14.12
	Phosphate Buffer (SIF)	61.00 ± 3.30	0.43	+14.08

Transmission Electron Microscopy (TEM) of NGN

TEM analysis of the NGN L-SMEDDS formulation, after dilution with distilled water, revealed the formation of well-defined, spherical oil globules. These globules were uniform in size and shape, confirming the efficient emulsification and stability of the nanoemulsion. The even distribution of the globules supports consistent drug delivery and prevents phase separation. The TEM results align with the droplet size analysis, highlighting the formulation's potential for improved drug solubility, rapid release, and enhanced bioavailability. as shown in figure 01.

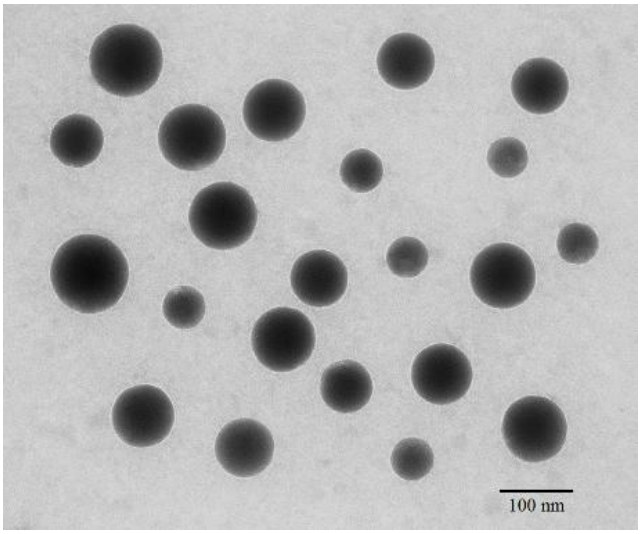

Fig 01: TEM image obtained from 1000-fold dilution of NGN L-SMEDDS (RLS2)

Cumulative Drug Release of NateglinideNGN L-SMEDDS

The cumulative release of Nateglinide (NGN) was assessed in 0.1N HCl, SAB at pH 4.5, and SGF at pH 6.8. SGF showed the highest release, reaching 93.45% at 60 minutes, followed by SAB at 93.19%. 0.1N HCl had the lowest release, though still effective. These results suggest NGN L-SMEDDS performs best in neutral to slightly acidic conditions, ideal for intestinal absorption, as shown in Figure 02.

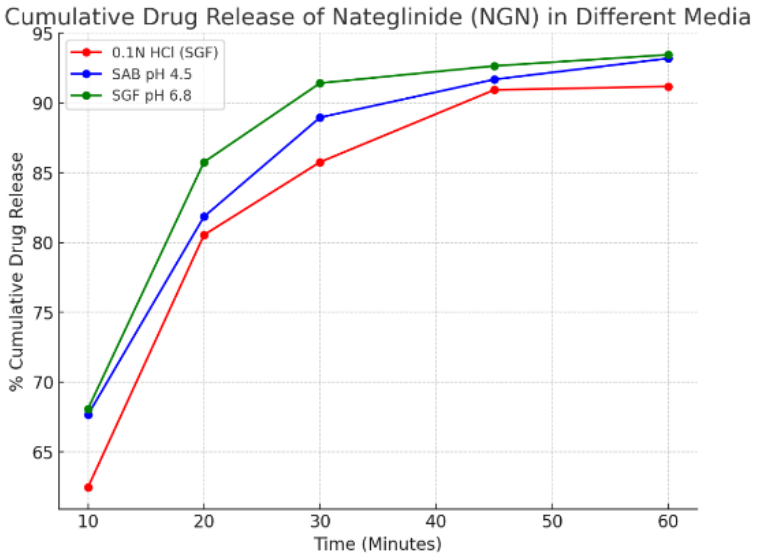

Fig 02: In Vitro Dissolution Profile of NGN L-SMEDDS in Various Dissolution Media

Physical Property of P-SMEDDS of NGN

The P-SMEDDS formulation demonstrated excellent flow properties, with an angle of repose of 22º23', a Carr's Index of 7.71%, and a Hausner Ratio of 1.08. Neusilin US2 exhibited a high binding capacity of 2000 mg/g, which facilitated the efficient transformation of L-SMEDDS into a free-flowing powder with a target dose of 375 mg of NGN, as shown in Table 03.

Table 03: Comparison of adsorbing agents for their binding capacity and flow properties

Parameter	**Observation**
Binding Capacity of Neusilin US2 (mg/g)	2000
Angle of Repose	22º23'
Bulk Density (BD) (g/mL)	0.323 ± 0.015
Tapped Density (TD) (g/mL)	0.350 ± 0.010
Carr's Index (%)	7.714 ± 0.10
Hausner Ratio	1.08
P-SMEDDS Equivalent to Target Dose of NGN (mg)	375.00

***In vitro* dissolution profile of NGN P-SMEDDS**

The dissolution profile indicates that drug release was significantly influenced by the pH of the dissolution media. At all time points, higher drug release was observed in SAB pH 4.5 and PB pH 6.8 compared to 0.1N HCl, suggesting enhanced solubility in mildly acidic and near-neutral environments. After 60 minutes, the cumulative drug release reached approximately 94% in SAB pH 4.5 and 93% in PB pH 6.8, while only 87% was released in 0.1N HCl. These results demonstrate the formulation's improved dissolution behavior in intestinal-like conditions as shown in Figure 03.

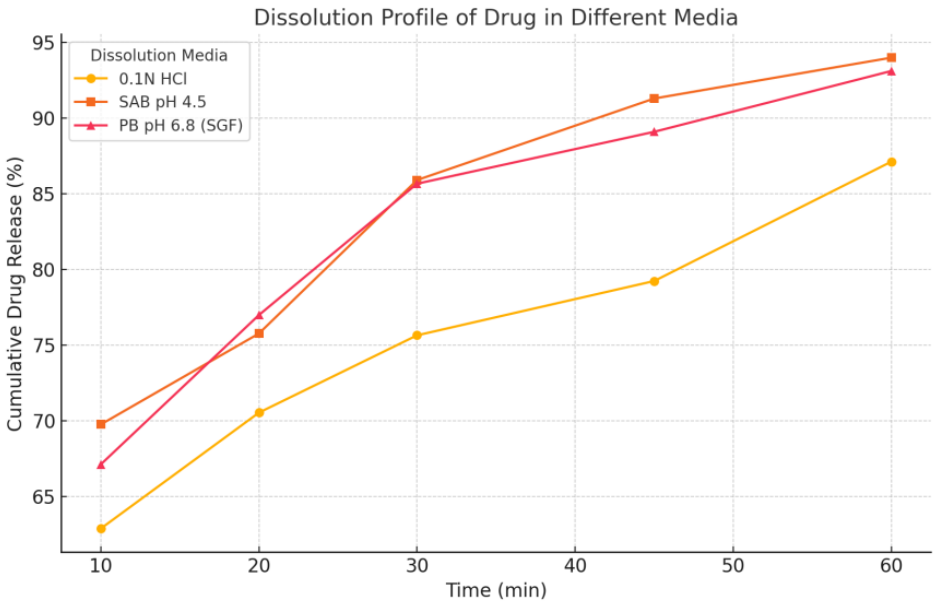

Figure 03: *In vitro* dissolution profile of NGN P-SMEDDS

Development of NGN T-SMEDDS

The optimized NGN T-SMEDDS tablets were prepared using Crospovidone (2.5% w/w) as the disintegrant, blended with MCC, Neusilin US2 (carrier), Magnesium Stearate, and Talc. A uniform blend was achieved through sequential mixing, followed by compression using a 12 mm punch under sufficient pressure to maintain tablet hardness between 4–4.5 kg/cm². The final formulation contained 375 mg NGN, ensuring good mechanical strength, flow, and rapid disintegration. Post-compression, tablets were subjected to standard quality control tests to ensure uniformity and performance.

Evaluation Parameters for T-SMEDDS of NGN

From the evaluation data, samples 1 to 7 exhibited smooth surface appearance with acceptable hardness (4.5–5.3 kg/cm²) and friability below 1%, indicating good mechanical integrity. Disintegration time decreased progressively, with sample 6 showing the shortest time (7 min) among smooth tablets. Samples 8 to 10 disintegrated rapidly in less than 5 seconds but had a rough surface and were not tested for hardness or friability, suggesting poor mechanical properties despite rapid disintegration. Sample 6 demonstrated an optimal balance between physical integrity and disintegration performance. (Table 04)

Table 04: Evaluation Parameters for T-SMEDDS of NGN

	Sample									
Parameter	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**
Surface appearance	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Smooth	Rough	Rough	Rough
Hardness (kg/cm²)*	5.3	4.8	4.8	4.9	4.5	5.0	4.8	Not Done	Not Done	Not Done
Disintegration Time* (min)	28	17	9	14	10	7	10	<5s	<5s	<5s
Friability (%)	0.31	0.42	0.41	0.41	0.56	0.51	0.49	Not Done	Not Done	Not Done

***In vitro* dissolution profile of NGN T-SMEDDS**

The cumulative drug release of Nateglinide (NGN) T-SMEDDS was evaluated in three media—0.1N HCl (SIF), SAB pH

4.5, and PB pH 6.8 (SGF)—to simulate GI tract conditions. The optimized T-SMEDDS showed improved release in SAB pH 4.5 (67.10% at 60 min), followed by 0.1N HCl (62.56%) and PB pH 6.8 (53.52%), indicating enhanced solubility in mildly acidic conditions. In comparison, the marketed T-SMEDDS showed a slightly lower release profile, with maximum release in SAB (64.15%) and comparatively lower values in 0.1N HCl (58.05%) and PB (50.87%). Overall, the optimized T-SMEDDS demonstrated superior dissolution performance across all media, particularly under acidic pH, which is beneficial for improving NGN bioavailability in upper GI regions as depicted in figure 04.

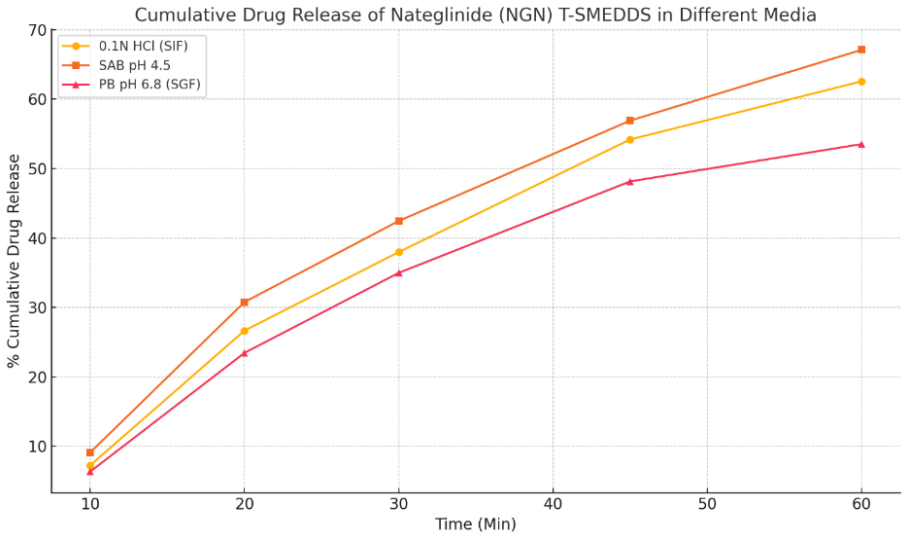

Figure 04: *In vitro* dissolution profile of NGN T-SMEDDS

3. DISCUSSION

The present study successfully developed and optimized a solid self-microemulsifying drug delivery system (S-SMEDDS) for nateglinide, aimed at overcoming its poor aqueous solubility and enhancing its oral bioavailability [20,21]. Nateglinide's limited and erratic absorption, due to its low solubility and extensive hepatic first-pass metabolism, presents a significant challenge in effective diabetes management [22]. In this study, Capryol 90 was selected as the oil phase due to its superior drug solubilization capacity, while Cremophor RH 40 and Transcutol P served effectively as surfactant and co-surfactant, respectively. These excipients facilitated the formation of a stable microemulsion system with optimal self-emulsification efficiency [23,24]. The pseudo-ternary phase diagram confirmed a wide microemulsion region, indicating robust emulsification potential. The optimized liquid SMEDDS was adsorbed onto Neusilin US2, a porous carrier, to obtain a solid, free-flowing powder that retained the self-emulsifying properties of the original system [25,26]. Characterization studies revealed a nano-sized droplet diameter (158.3 ± 4.2 nm), low polydispersity index, and negative zeta potential, all indicative of a stable microemulsion system upon reconstitution [27]. FTIR, DSC, and XRD analyses confirmed the absence of drug–excipient interactions and demonstrated the transformation of nateglinide to an amorphous state, contributing to improved solubility. The in vitro dissolution profile showed over 90% drug release within 30 minutes from the S-SMEDDS, significantly surpassing the pure drug and marketed formulation, which supports enhanced dissolution and likely improved bioavailability [28, 29]. Furthermore, the formulation remained stable over three months under accelerated conditions. These results highlight the potential of S-SMEDDS as a promising strategy for improving the therapeutic performance of poorly water-soluble antidiabetic drugs like nateglinide[30-43].

4. CONCLUSION

The development and optimization of nateglinide-loaded Solid SMEDDS significantly improved the solubility and bioavailability of this poorly water-soluble antidiabetic drug. By optimizing key excipients and formulation parameters, the study demonstrated enhanced drug release and absorption, overcoming the solubility limitations of nateglinide. The solidified SMEDDS formulation provided advantages in terms of stability, handling, and scalability, making it a promising approach for improving the therapeutic efficacy of nateglinide in type 2 diabetes management. Future studies, including in vivo pharmacokinetic evaluations, are necessary to further validate its clinical potential and optimize the formulation for patient-specific applications

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