DEVELOPMENT AND IN-VITRO CHARACTERIZATION OF A VILDAGLIPTIN AND METFORMIN SMEDDS (VILDAFORMIN) FOR THE MANAGEMENT OF TYPE-2 DIABETES

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How to cite this article: Sharma V, Gautam H, Kumar G. Development and In-Vitro Characterization of a Vildagliptin and Metformin SMEDDS (VILDAFORMIN) for the Management of Type-2 Diabetes. Int J Drug Deliv Technol. 2026;16(14s): 781-797. DOI: 10.25258/ijddt.16.14s.91
Source of support: Nil.
Conflict of interest: None

ABSTRACT

Background: For managing Type 2 Diabetes Mellitus, the combination treatment with drugs such as Vildagliptin and Metformin are often used; however, they both have poor solubility and dissolution profiles, affecting their therapeutic efficacy.

Objective: This study developed, optimized, and evaluated a Self-Microemulsifying Drug Delivery System (SMEDDS) for the combined delivery of both Vildagliptin and Metformin (Vildaformin).

Methods: Using a Central Composite Design (CCD), five formulations (A1-E5) were developed from White Sesame oil, Polysorbate 80, and Propylene Glycol. Characterization included FTIR studies, Molecular Docking, in vitro dissolution at pH 1.2 and 6.8, Transmission Electron Microscopy (TEM), and 6-month accelerated stability studies.

Results: Among those, E5 was the optimized formulation with a Z-average droplet size of 84.05 nm, polydispersity index of 0.294, and a Zeta potential of -17.9 mV, proving that it has good electrokinetic stability. FTIR and Molecular Docking confirmed the drugs were compatible chemically within the matrix; docking showed a high binding affinity for Vildagliptin (-6.3 kcal/mol) due to the adamantyl hydrophobic anchor. In vitro dissolution showed that the SMEDDS formulation gave >88% dissolution vs <68% dissolution of the conventional tablets over 120 minutes. TEM confirmed nanoglobules are uniformly spherical in shape. According to 6-month accelerated stability results, E5 remained stable with little to no change in drug content or droplet size due to a solid mechanical barrier at the oil-water interface.

Conclusion: The optimized Vildaformin SMEDDS represent a viable means of providing a more stable and potentially increased bioavailability of the diabetes medicine by providing an optimally formulated means of improving the oral delivery of this antidiabetic drug combination, making it suitable as an alternative delivery system.

Keywords: Vildagliptin-Metformin FDC, Self-microemulsifying Drug Delivery System, Central Composite Design, Molecular Docking, Improved Bioavailability, Thermodynamic Stability.

1. INTRODUCTION

A major barrier in delivering drugs via the oral route is the poor solubility of many active pharmaceutical ingredients (APIs), which can lead to inconsistent absorption rates and lack of therapeutic effect as shown by one recent study. Even though patients generally prefer taking medication orally, when an API does not dissolve adequately in gastric secretions, this route may not be appropriate for that particular API [1,2]. Recently, the use of lipid-based carriers such as self-microemulsifying drug delivery systems (SMEDDS) has been proposed as an effective way to improve oral bioavailability. SMEDDS are unique systems formed by mixing surfactants, APIs, oils and co-surfactants into an isotropic solution that upon gentle agitation in the GI tract will spontaneously separate into fine oil-in-water microemulsions [3]. SMEDDS also provide thermodynamic stability and allow for the dissolution rate-limiting step to be bypassed, making them particularly valuable systems for orally administering poorly soluble compounds (i.e. APIs) of BCS Class II and IV (as shown in two recent studies) [4,5]. This is of particular concern with approximately 500 million people worldwide suffering from diabetes mellitus (DM) [6]. Diabetes mellitus Type 2 is characterized by insulin resistance and chronic elevated blood glucose levels [7,8]. Metformin (biguanide) and vildagliptin (DPP-4 inhibitor) are often prescribed together in fixed dose combination (FDC) formulation for optimal glycemic control [9,10].

However, the poor aqueous solubility of metformin/vildagliptin limits their absorption in the body when taken orally as separate entities. An innovative approach to address the poor absorption of the metformin/vildagliptin FDC has been to formulate them into a SMEDDS called vildaformin-SMEDDS, which allows these two medications to be combined in a pre-solubilized form for improved clinical outcomes [11].

2. MATERIALS AND METHODS

2.1. Materials: Vildagliptin and Metformin hydrochloride were obtained from Tagoor Laboratories Pvt. Ltd., Andhra Pradesh, India. Castor oil, olive oil, sesame oil, coconut oil, sunflower oil, Brij 35, Tween 80 (Polysorbate 80), sodium lauryl sulfate (SLS), ethanol, polyethylene glycol (PEG), glycerol, propylene glycol, and 2-propanol were obtained from Him Laboratory, Solan, Himachal Pradesh, India. All chemicals used were of analytical reagent grade.

2.2. Methods: Pre-formulation Studies

2.2.1. Solubility Studies: The solubility of metformin and vildagliptin via shake-flask method was carried out by adding an excess number of each drug to a total of 2 ml of different types of oils, surfactants and co-surfactants. The mixtures were agitated using a cyclomixer for 10 minutes then allowed to equilibrate at room temperature for 72 hours. After that, the samples were centrifuged at 2700 rpm for 15 minutes; then, the supernatants were filtered with a 0.45 µm membrane filter for HPLC analysis [12, 13].

2.2.2. Assessment of Oils: In order to screen oils for their ability to solubilize API, the shake flask method was used. Each oil was supplemented with an additional amount of API, and mixed for 10 minutes on a cyclomixer to achieve homogeneous blends. The blended samples were each allowed to equilibrate at room temperature for 72 hours before being placed in a centrifuge and spun at 2700 rpm for 15 minutes. The resulting supernatants were analyzed using HPLC to identify the oil vehicle that could solubilize the most API [14,15,16].

2.2.3. Selection of a Surfactant: To examine the best surfactant for emulsifying, basic (aerosol) testing was used to find an emulsifying/surfactant prepared for testing. The oil emulsion surfactants (with 0.3 grams surfactant) were added to the oil phase, which had been chosen, mixed together for 120 seconds in a vortex, and then placed in a 40-45°C hot water bath for 30 seconds. Afterwards a 50mg uniform mixture of the emulsion and measured at an incrementally higher volume of water was added to the container and placed in a vial, (each representing a different surfactant). The resulting emulsions were evaluated for the

relative ease of emulsion formation (by inverting the vials) and the emulsions remained at room temperature for two hours prior to evaluation. The selection of the appropriate surfactant was based on their capacity to generate an emulsion that was clear and had high levels of transmittance, and had the fewest number of inverted vials [17,18].

2.2.4. Co-Surfactant Screening: The emulsifying ability of different co-surfactants was assessed after performing an oil screening. To create an isotropic mix, 0.2 g of each co-surfactant and 0.3 g of oil phase were weighed together, added into a vortex mixer for two minutes, then heated at 40-45 ° C for 30 seconds. Distilled water was used to dilute to 50mL using a volumetric flask. The number of inversions to create a clear emulsion was counted. Co-Surfactant was selected based on achieving maximum transmittance with the least inversions having allowed two hours for the emulsion to settle [19].

2.2.5. HPLC of Vildaformin in Oil: An Agilent 1260 Infinity Series HPLC System (including a C-18 analytical column 4.6mm ID × 150mm) was used for the analysis. The column oven temperature was kept constant at 80°C. The method used binary gradient mode with a mobile phase consisting of acetonitrile and 0.010M orthophosphoric acid (50%/50% by volume) at a flow rate of 0.900 mL/min. Analytes were detected using a variable wavelength detector (VWD) set to 240 nm [20,21].

2.2.6. Ternary phase diagram construction: The pseudo-ternary diagrams used to create an optimal region for microemulsions were constructed using nonaqueous mediums (oil and surfactant) and aqueous mediums (water). The pseudo-ternary diagrams were created by determining the amount of surfactant and water necessary to create an isotropic mixture at room temperature (25º C). This was accomplished by preparing surfactant mixtures (Smix) to yield varying weight ratios (e.g., 1:1, 2:1, 3:1) of the surfactant and co-surfactant in Eppendorf tubes. The Eppendorf tubes containing the Smix were then vortexed for five minutes, followed by a one-hour incubation at 50°C. The next step in creating the pseudo-ternary diagram was determining the weight ratio of surfactant to oil at ratios from 1:9 through 9:1. After the surfactant and oil were combined, the mixture was vortexed for five minutes, followed by one hour of incubation at 50°C. After the surfactant/oil mixture had been vortexed, dropwise addition of water from 0 to 100% was made under magnetic stirring until the solution changed from clear to cloudy. The cloudy to clear transition represented the upper and lower boundaries of the microemulsion [22].

2.2.7. Drug excipient compatibility studies: FTIR spectra of Metformin HCl, Vildagliptin HCl, and their combinations were obtained using a PerkinElmer spectrophotometer. Potassium bromide (KBr) disk samples were scanned at a resolution of 4 cm^{-1} over a spectral range of 400–4000 cm^{-1} [23,24].

2.2.8. SMEDDS Preparation Method: A SMEDDS formulation consisting of White Sesame oil, Tween 80 (surfactant), and Propylene Glycol (co-surfactant) was developed. The drugs were initially dissolved in the oil phase, after which the surfactant and co-surfactant were weighed and mixed via a magnetic stirrer for 5 minutes. The S_{mix} was placed in a hot air oven at 50°C for 1 hour. The drug-oil mixture was then incorporated into the S_{mix} and stirred for 5–10 minutes at 50°C to form an isotropic mixture. The final formulation was sonicated until a clear solution was achieved [25,26,27].

2.3. Optimization of Formulation using Central Composite Design (CCD): The concentration of oil and S_{mix} was optimized using a Central Composite Design (CCD) via Design Expert software (Version 13, Stat-Ease Inc., USA). The SMEDDS was generated by varying the amounts of oil (mg) and S_{mix} (mg), which were defined as the independent variables. The dependent variables (responses) selected for the study included globule size, percentage transmittance, and polydispersity index (PDI).

The levels for these independent variables were established based on the results obtained from the pseudo-ternary phase diagrams. According to the CCD requirements, a total of 13 formulation runs were conducted, comprising five center points, four factorial points, and four axial points. The independent and dependent variables used in the experimental design are summarized in Table 1 [28,29].

3. EVALUATION PARAMETERS OF SMEDDS

3.1. Visual inspection, Phase separation and extent of visibility: The efficiency of self-emulsification was assessed by diluting the type of formulation SMEDDS with a volume of 200 mL distilled water at 37 degrees Celsius. A milky/opaque appearance indicated the formation of a macroemulsion; while an isotropic/transparent solution indicated the formation of a microemulsion. The diluted mixture was visually assessed over 24 hours for phase separation or drug precipitation [30].

3.2. % Transmittance and Viscosity: Using a UV-Vis spectrophotometer, a 1:100 dilution was used to determine the percentage transmittance at 638nm and a Brookfield Rheometer (Spindle No. 6) was used to determine the viscosity of the Vildaformin SMEDDS at a rotation speed of 100rpm for 5 minutes [31].

3.3. Robustness to Dilution and Cloud Point: SMEDDS were diluted 50, 100, and 1000-fold in three different media (0.1 N HCl, distilled water and PBS pH 7.4). The physical properties of the products were assessed over 6 hours for changes. The cloud point of a diluted SMEDDS (1:50) was determined by heating in a water bath at 10°C/min until turbidity was visible [32,33].

3.4. Thermodynamic Stability: Stability was investigated through six heating-cooling cycles between 4°C and room temperature, with storage at each temperature for at least 48 hours. Formulations that passed these cycles were further subjected to centrifugation tests [34,35].

3.5. Zeta Potential, Particle Size, and Refractive Index: Zeta potential was measured using a Litesizer 500 in triplicate. Particle size and polydispersity index (PDI) were determined via Dynamic Light Scattering (DLS) to estimate the distribution and Brownian motion of the droplets. Drug loaded SMEDDS refractive index was determined using an Abbe type thermos defined refractometer [33,34].

3.6. In-vitro Dissolution Studies: Release tests were carried out using a modified USP XXIV method in 0.1 N HCl (pH 1.2) and PBS (pH 6.8) at 37 ± 0.5°C. Samples were filled into pre-treated dialysis bags and rotated at 100 rpm. Aliquots were withdrawn periodically, replaced with fresh media to maintain sink conditions, and quantified via UV-spectrophotometry at 230–235 nm [16,36].

3.11. Drug Molecule Docking: The 3D structures of the drugs were obtained from the PDB. Vildagliptin was docked against DPP-4 (PDB ID: 2ONC), and Metformin was docked against AMPK (PDB ID: 4CFE). Orientational spatial structures were minimized using Avogadro force fields, and protein-drug interactions were validated using PyMOL [37].

3.12. Morphology (TEM) Studies: The morphology of the optimized SMEDDS was authenticated using Transmission Electron Microscopy (TEM) [38].

3.13. Stability studies: Stability tests were conducted according to ICH guidelines at 25°C/60% RH and 40°C/75% RH for up to 6 months [36].

4. RESULT

4.1. Pre-formulation Studies

4.1.1. Screening of Excipients: The screening of oils included the following options: Olive Oil, Castor Oil, Sunflower Oil, Coconut Oil, and White Sesame Oil. The two drugs were able to dissolve in Castor Oil, Olive Oil, and White Sesame Oil; therefore, whichever oil has the best capacity to load both drugs and measured by HPLC (High Performance Liquid Chromatography) was selected. Surfactants used in this study were Brij 35, Sodium Lauryl Sulphate (SLS), and Tween 80. To assess emulsification efficiency, each surfactant's % Transmittance and A (Absorbance) at 240 nm were measured. This frequency was selected due to the equivalent amount of the surfactant and light interacting in a UV Wavelength and each surfactant had a different %A – SLS %A at (0.225), Tween 80 %A at (0.099) and Brij 35 %A at (0.048).

In regard to the properties of co-surfactants, Propylene Glycol exhibits the most favourable properties with respect to both low absorbance and maximum transmittance. Therefore, Propylene Glycol is considered to be superior in

terms of its ability to remain clear within a SMEDDS system (i.e., medium, oily and surfactant component). On the other hand, Ethanol and 2-Propanol demonstrated greater absorbance than Propylene Glycol, which will not allow for their use in those formulations where clarity is very important. Glycerol produced a moderate level of clarity, providing an acceptable level of transmittance; however, because of its level of absorbance, Glycerol will likely interfere with optical clarity. Based upon these observations, Propylene Glycol has been chosen as the best co-surfactant for continued product development. The comparative solubility and clarity profiles of the surfactants and co-surfactants used in these experiments are shown in Figure 1.

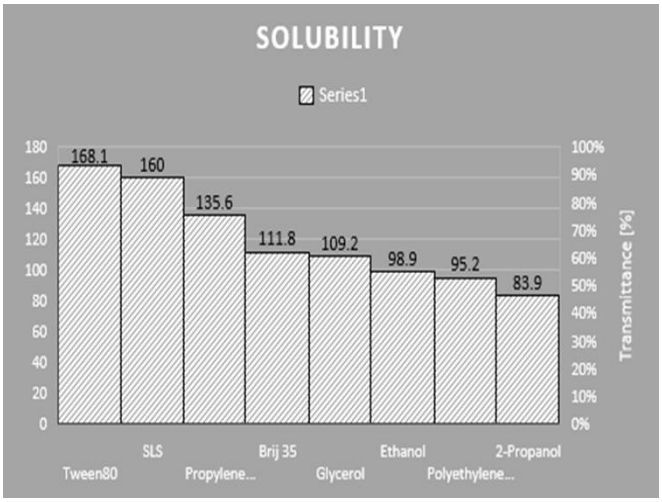

Figure 1. Solubility profile of different surfactants and co-surfactants in terms of % transmittance and absorbance values

4.1.2. HPLC Analysis of Vildaformin in Oil: When compared with the other two oils, Olive Oil and Castor Oil, White Sesame Oil was determined to be the preferable vehicle. The Sesame Oil chromatographic profile had much fewer extraneous peaks, indicating that the oil had a higher level of purity than the other oils. This is important for the success of the SMEDDS development, as the use of highly purified oils promotes better self-emulsification than oils of lower purity and aids the overall formula performance. The chromatogram that was developed for the mixture of the Sesame Oil and drug recorded at 240 nm had distinct peaks corresponding to the various components within the mixture of the Sesame Oil and drug. The analytical parameters of the various chromatographic components were used to verify the reproducibility of the results by using the retention time, area of peak, area of peak % and height of peak. A summary of the chromatographic data, including the comparisons of the chromatographic parameters is included in Figure 2 and Table 1, respectively.

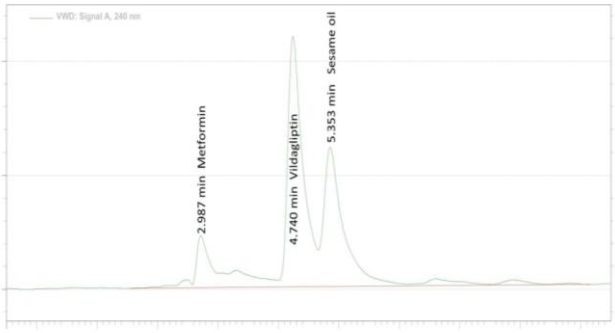

Figure 2. HPLC chromatogram of Vildaformin SMEDDS in sesame oil showing major peaks and retention Time of drugs and sesame oil.

Table 1: HPLC data of vildaformin SMEDDS formulation.

Drug/Compound	Retention Time	Area	Area %	Height	Height %
Metformin	2.987	75774	1.07	5875	1.60
Vildagliptin	4.740	3219363	45.34	184402	50.25
Sesame oil	5.353	2349060	33.08	102532	27.94

4.1.3. Pseudo-Ternary Phase Diagrams: Pseudo ternary phase diagrams were developed to map the boundaries of the three product phase regions, O & W, Bi-Continous and W & Oil. There is a noticeable curve to the phase boundary separating each product type. As the concentration of surfactants was increased, micro-emulsions became more stable. In Figure 3, we were able to identify a region of micro-emulsion, which relates to the equilibrium of SMIX, oil, and water. There were specific SMIX ratios at which the greatest area covered by the micro-emulsion was observed; therefore we used these ratios to guide us in selecting final concentrations for our SMEDDS formulations.

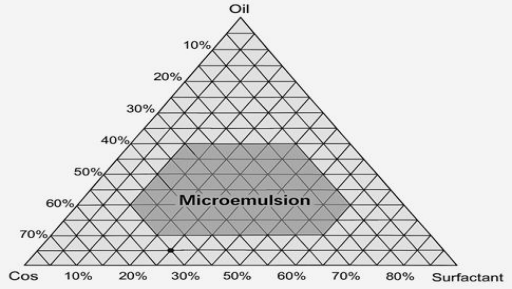

Figure 3. Ternary phase diagram depicting the microemulsion region for varying surfactant, co-surfactant, and oil ratios.

4.1.4. FTIR Spectral Analysis of Metformin Hydrochloride: The Metformin Hydrochloride is a biguanide and has been confirmed using an FTIR spectrum through several diagnostic peaks. Sharp distinctive peaks between 3368cm-1 and 3291cm-1 indicate the N-H stretching of the primary amine groups and the 3148cm-1 peak suggests the secondary amine stretch. The strong absorption band at 1623 cm-1 signifies the C=N stretch of the imine group of the biguanide and is a key diagnostic peak. The peaks at 1560 cm-1 and 1474 cm-1 demonstrate N-H bending and C-N stretching respectively. The N-H wagging and out of plane bending bands in the 936cm-1 to 735cm-1 regions confirm the above statement. The quality checks pass and clear & clean peaks as compared against standard reference data indicated that this is a high purity sample of Metformin Hydrochloride. The FTIR spectra and chemical structure of Metformin Hydrochloride are shown in figure 4.

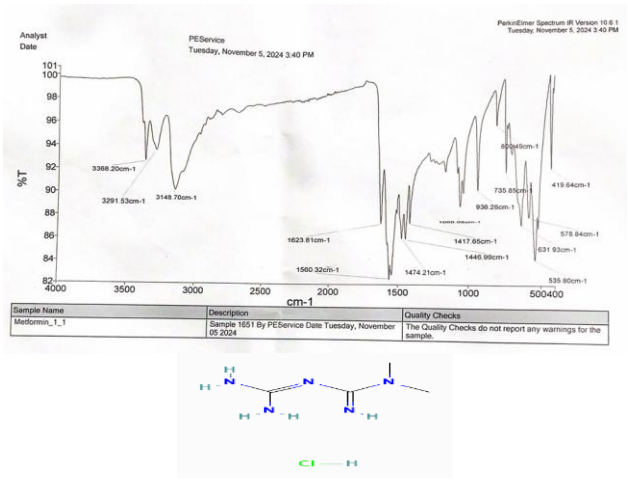

Figure 4. FTIR spectrum and chemical structure of the Metformin Hydrochloride (PubChem CID: 14219).

4.1.5. FTIR Spectral Analysis of Vildagliptin Hydrochloride: FTIR analysis depicts the chemical nature of the Vildagliptin Hydrochloride molecule via the various functional groups that are responsible for its activity as a cyanopyrrolidine antidiabetic agent. The peaks at 2914 cm-1 and 2845 cm-1 represent the asymmetric and symmetric stretching of the aliphatic C-H bonds in the adamantyl and pyrrolidine rings. The C=O stretching of the lactam (secondary amide) group is characterized by a highly diagnostic peak (1655 cm-1). The N-H bending and C-N stretching activity, which represent the amino-amide bond, is found in the 1560 cm-1 and 1404 cm-1 region. In addition, while Vildagliptin contains a nitrile moiety, which is typically observed as a sharp peak between 2200-2260 cm-1, it may be weak in certain forms of HCl salts, depending on the crystal state of the sample. Additionally, in the fingerprint region, there are many vibrations involved with the skeletal structure of C-C and C-N bonds, such as at 1053 cm-1, that are characteristic of the complex cage structure of the adamantyl moiety. The FTIR Spectra of Vildagliptin Hydrochloride and its corresponding chemical structure are shown in Figure 5.

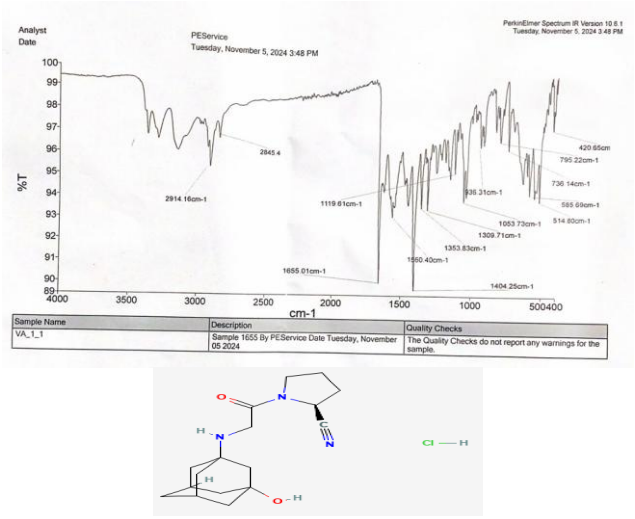

Figure 5. FTIR spectrum and chemical structure of Vildagliptin hydrochloride (PubChem CID: 16070539).

4.1.6. FTIR Spectral Analysis of Vildagliptin-Metformin Combination: We performed FTIR spectroscopy of the physical combination of Metformin and Vildagliptin (shown in Figure 6)

to identify any signs of compatibility and to find out if there were any common functional groups present in the tested samples. The FTIR spectrum results show that the Metformin hydrochloride and Vildagliptin hydrochloride combination forms a unique molecular 'fingerprint' where most of the individual diagnostic peaks for each drug can still be seen, indicating that there appears to be minimal chemical interactions between metformin and vildagliptin in this sample. In the high frequency region, there is a broad absorption peak located at 3293.76 cm-1 due to the superimposition of N-H stretching vibrations due to the biguanide (metformin) and the amino groups of Vildagliptin. There are also aliphatic C-H stretching bands due to the adamantyl cage of Vildagliptin visible at 2914.48 cm-1 and 2848.97 cm-1. In the spectrum's fingerprint region, one of the most prominent distinguishing features of this mixture is the sharp, narrow peak located at 1655.10 cm-1 due to the C=O amide bond of Vildagliptin. The fingerprint portion of the spectrum contains a large number of peaks (1403.56 cm-1 and 1053.25 cm-1) that correspond to various C-N and C-C skeletal vibrational frequencies present in both Metformin and Vildagliptin. In general, the composite spectrum looks similar to the synthesis spectra for both drugs and the 'Quality Checks' returned no warning messages, suggesting that the physical mixture is stable and includes pure substances.

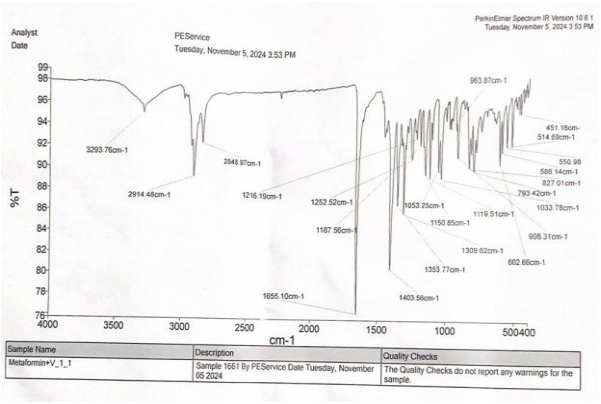

Figure 6. FTIR spectrum of Vildagliptin–Metformin physical mixture.

4.2. Formulation of Vildaformin SMEDDS

A total of five Vildaform SMEDDS formulations were developed with various ratios of Vildagliptin, Metformin, and excipients (White Sesame Oil [oil], Polysorbate 80 [surfactant] and Propylene Glycol [co-surfactant]). The detailed composition (formulation codes, A1 via E5) can be found in Table 2. The oil/surfactant ratios were systematically modified to develop the self-emulsifying properties of the formulation and optimise the system's drug loading capacity.

Table 2. Formulation Table of Vildaformin SMEDDS.

Chemicals	A1	B2	C3	D4	E5
Vildagliptin (%)	0.03	0.036	0.035	0.06	0.033
Metformin (%)	0.3	0.361	0.348	0.601	0.332
Sesame Oil (%)	19.63	19.61	24.91	13.91	11.07
Polysorbate 80(%)	51.1	51.06	56.03	71.54	66.42
Propylene Glycol (%)	28.94	28.92	18.67	13.91	22.14

4.3. Optimization and ANOVA Analysis of Vildaformin SMEDDS

A Central Composite Design (CCD) was employed to optimize the formulation variables of the Vildaformin Self-Microemulsifying Drug Delivery System (SMEDDS), with the primary goal of achieving the minimum droplet size. The independent variables selected for this study were (A) White Sesame oil, (B) Tween 80 (Surfactant), and (C) Propylene Glycol (Co-surfactant). Based on preliminary screening, the experimental ranges for these components were established as follows: oil concentration ranged from 11.07 to 24.91 mg, surfactant from 51.06 to 71.54 mg, and co-surfactant from 13.91 to 28.94 mg as shown in Table 3. A rotatable CCD with an alpha value (alpha) of 1.682 was utilized, generating a total of 20 experimental runs comprising factorial, axial, and center points to evaluate the response surface.

Table 3. Validation parameters of optimized formulation (E5).

Component	Optimized Composition (% w/w)
Sesame oil	11.07
Tween80 (Surfactant)	66.42
Propylene glycol (Co-surfactant)	22.14

4.3.1. Central Composite Design Matrix: The following table (Table 4) is the coded and real levels of the CCD runs were utilized in fitting and validation of the model.

Table 4. Central Composite Design for Formulation Optimization.

Run	A (coded)	B (coded)	C (coded)	Oil (A) (%)	Surfactant (B) (%)
1	-1	-1	-1	11.07	51.06
2	-1	-1	+1	11.07	51.06
3	-1	+1	-1	11.07	71.54
4	-1	+1	+1	11.07	71.54
5	+1	-1	-1	24.91	51.06
6	+1	-1	+1	24.91	51.06
7	+1	+1	-1	24.91	71.54
8	+1	+1	+1	24.91	71.54
9	+α	0	0	29.63	61.30
10	-α	0	0	6.35	61.30

4.3.2. Surface Response and Contour Plot: The influence of oil and surfactant concentrations on the resulting droplet size is illustrated through the contour and 3D surface plots in Figure 7 and Figure 8 respectively. For this analysis, the co-surfactant concentration was maintained at its midpoint (21.425%).

The data indicate there was a decrease in droplet size as the surfactant concentration increased, especially for moderate amounts of oil added to the oil/surfactant mixture. Therefore, when the surfactant-to-oil ratio was greater, interfacial stabilization improved and resulted in the production of finer microemulsions. On the contrary, with lower levels of surfactant and an increase in oil concentration, the size of the droplets increased as expected. This was likely due to a lack of surfactant coverage at the oil-water interface causing the oil to not be included in the formation of microemulsions.

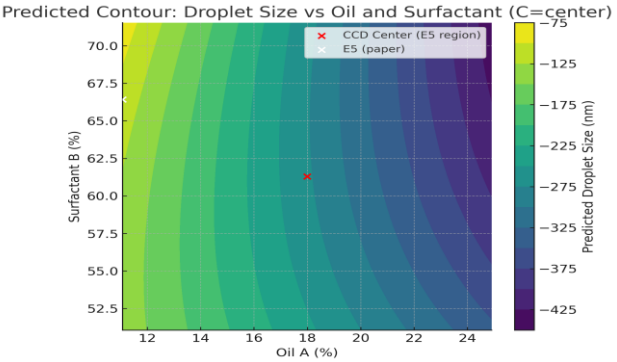

Figure 7. Contour plot: Droplet size vs Oil and Surfactant.

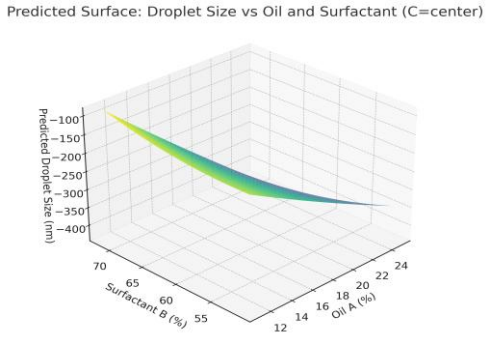

Figure 8. Surface plot: Droplet size vs Oil and Surfactant.

4.3.3. FTIR Analysis of SMEDDS Formulation: The formulation of a self micro emulsifying drug delivery system with metformin Hcl and vildagliptin Hcl using FTIR spectroscopic analysis (Figure 9). The final formulation showed all of the known chemical properties of both drugs-the C=O amide stretching of vildagliptin Hcl is at 1655.38 cm-1, while the C=N imine stretching of metformin HCl is shown to be at 1623 cm-1. The significant widening and shift of the N-H stretching peak to higher wavenumbers (3389.30 cm-1) indicates strong hydrogen bonding interactions were formed between the two drug molecules and the hydrogen donating hydroxyl groups found in the excipient's propylene glycol and Tween 80, respectively. The presence of the ester carbonyl peak (1735.82 cm-1) indicates that sesame oil and Tween 80 were successfully integrated into the formulation. There were no new/unexpected peaks or significant adverse shifts detected in the FTIR spectrum, thus confirming that the drugs were properly encapsulated within the formulation

matrix while remaining chemically compatible with all other materials used to create the formulation resulting in a stable delivery system.

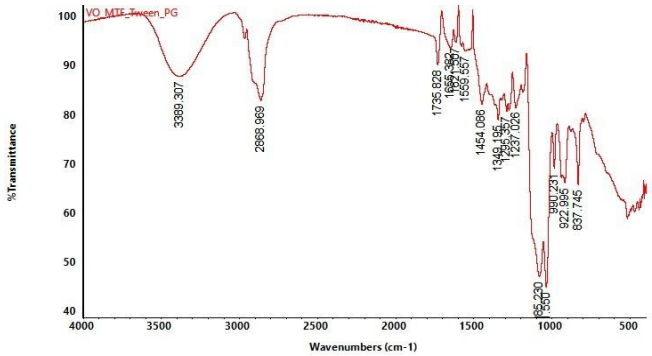

Figure 9. FTIR spectrum of SMEDDS formulation containing Vildagliptin and Metformin.

4.4. Evaluation Parameter of Vildaformin SMEDDS

4.4.1. Visual Inspection and Emulsification Grading: The developed Vildaformin SMEDDS formulations were initially observed as clear, pale-yellow solutions. Following a 1:100 dilution with distilled water, the systems were monitored for phase separation and drug precipitation using a standardized visual grading system (Grades A to E).

Formulations A1, B2, and C3 exhibited rapid phase separation and drug precipitation. According to the visibility grading criteria summarized in Table 5, these formulations were assigned lower stability grades due to their lack of physical integrity upon dilution. In contrast, formulations that demonstrated no drug precipitation and negligible or no phase separation were considered physically stable. These stable systems were selected as suitable candidates for further characterization and stability studies, as they successfully maintained an isotropic state upon aqueous titration.

Table 5. Visible inspection of SMEDDS after dilution, phase separation, and precipitation results of prepared microemulsions.

	A1	B2	C3	D4	E5
Visibility grade	C	B	C	B	A
Phase separation	+	+	+	x	x
Precipitation	xx	xx	++	xx	xx

x: No phase separation, xx: No precipitation, + Phase separation, ++ Precipitation.

4.4.2. Percentage Transmittance: To check the self-microemulsifying ability and clarity of the SMEDDS, the percentage transmittance was measured at 638 nm using a UV-Visible spectrophotometer. For this analysis, the formulation was diluted 100 times with distilled water. It was found that the transmittance was 9.2%. A transmittance value above 98% is typical for isotropic microemulsion while the 9.2% value indicates the presence of a milky-opaque dispersion when tested under the above conditions. This characteristic was taken as a very important way of distinguishing whether the material would form as a microemulsion or as a coarser macroemulsion when diluted with water.

4.4.3. Analysis of Robustness to Dilution: Quality control of Vildaformin SMEDDS as a microemulsion was assessed over a range of physiological conditions represented in Table 6 to demonstrate stability through extreme dilution. The formulation showed no signs of phase separation or turbidity/precipitation due to drug in any condition tested (distilled water, 0.1 N HCl, PBS pH 7.4). Thus, the data support the ability of this formulation to maintain its integrity and suspend drugs in a solution regardless of how much gastic/intestinal fluid it encounters when administered.

Table 6. Emulsification times of different SMEDDS formulations in 0.1 N HCl and Phosphate buffer.

	0.1 N HCl			
Formulation Code	**Time of emulsification (s)**	**Emulsification tendency**	**Time of Emulsification (s)**	**Emulsification Tendency**
A1	19	Poor	20	Poor
B2	20	Poor	21	Poor
C3	25	Separated	24	Separated
D4	40	Good	26	Good
E5	50	Good	30	Good

4.4.4. Cloud Point Determination: Cloud point measurements were performed to assess the temperature stability of the microemulsion corresponding to physiological temperatures. When heated, the E5 SMEDDS diluted formulation stayed clear and transparent for the entire test temperature range. The first signs of cloudy formations were seen at approximately 55°C. Turbidity was reported as moderate and progressed no further than the formation of macro-phase separation during their time of observation. Since the cloud point for the optimized formulation (55 °C) is well above human body temperature (37°C), it would therefore be reasonable to expect continued integrity of the SMEDDS microemulsion and to prevent drug precipitation in response to the temperature of the gastrointestinal tract.

4.4.5. Thermodynamic Stability Study: The optimized formulation E5 was physically stable, clear and thermally stable after exposing to degradation temperatures (above or below) of the human body. No physical changes were noted in the formulation regardless of the thermal degradation conditions or after centrifugation to show successful stability during centrifugation testing. The absence of phase separation, creaming, or precipitated Vildaformin during the heating-cooling cycle further confirms the good thermodynamic and kinetic stability of the developed Vildaformin-SMEDDS. These results indicate that the product is able to withstand environmental stress during storage and transportation without compromising the stability of the microemulsion.

4.4.6. Measurement of Zeta Potential: The Zeta potential for the prepared SMEDDS formulas (A1, B2, D4, and E5) was determined by using a Litesizer 500 (Anton Paar, Austria)) based on droplet surface charges and droplet electrokinetic stability. The A1, B2, and D4 formulations provided evidence of poor electrostatic stability (i.e., high chance of droplet aggregation over time) versus the optimized formulation E5, which had a zeta potential of -17.9 mV (Figure10). This negative charge indicates good electrostatic stability due to the repulsive forces between the droplets and hence prevents droplet coalescence. The data indicates that formulation E5 has the appropriate physical properties for maintaining SMEDDS during storage and during transit through the physiology.

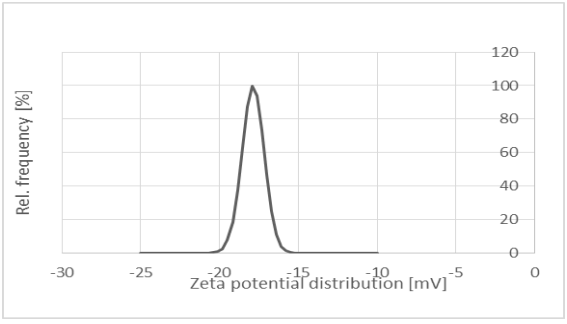

Figure 10. Zeta potential distribution graph of optimized E5 formulation.

4.4.7. Refractive index determination: Measurement of the oil's refractive index was performed following the description in the FSSAI's Manual on Analysis for Foods, Oils and Fats (2021) – Uni-Dimensional Optical Methods of Analysis document (02.003:2021). An Abbe refractometer at room temperature could measure the refractive index of the oil phase to be 1.453, which was then used for comparison to determine life products' overall quality based on their oil content using the same method and instrument through a qualitative comparison. Since the refractive indices were equivalent between the tested samples (i.e., Oil versus Oil Phase), the isotropic quality and optical clarity of the final product (the smedds) was validated.

4.4.8. Determination of Droplet Size and Polydispersity Index (PDI): Dynamic Light Scattering (DLS) measurements were taken at 25°C on a Litesizer 500 (Anton Paar, Austria), with the droplet sizes and polydispersity indices (PDIs) of the developed SMEDDS verified by DLS using a backscatter configuration and disposable cuvettes; the dispersant medium used was distilled water. The droplet size is an important parameter that will affect the in vivo disposition of the emulsion because the smaller the globule is (smaller globules dissolve and absorb better than larger ones). The Z-average diameter of the optimized SMEDDS formulation (E5) was determined to be 84.05 nm (see figure 11), which falls into the proper range for self-micro emulsification to occur.

The PDI measured 0.294 indicating that there is a narrow and uniform size distribution of the drops. This low PDI demonstrates that a monodisperse system was produced, an important factor in producing a repeatable drug release profile and stability.

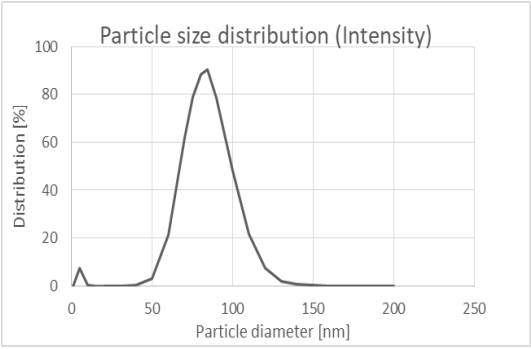

Figure 11. Dynamic Light Scattering (DLS) plot of the droplet size distribution of the E5 formulation

4.4.9. In-Vitro Dissolution Studies: The in vitro release of the Optimized Vildaformin (Vildagliptin) Self-Microemulsifying Drug Delivery System (SMEDDS) was compared to its conventional dose at both 0.1N HCl (pH 1.2) and Phosphate buffered solution (pH 6.8) over a 120 min period. The cumulative release profile of the Vildaformin SMEDDS was much higher than the conventional release in both media (See Figure 12). In the phosphate buffered solution (pH 6.8), the SMEDDS composition demonstrated that >92% and >88% of Metformin and Vildagliptin were released from the formulation, respectively. In comparison, only 68% and 53% of Metformin and Vildagliptin were released, respectively, from the conventional tablet at the end of the 120 min period. The trends noted at acid medium (pH 1.2) followed the same trends noted at neutral pH (6.8) thereby validating that the SMEDDS has a much greater potential for dissolution than the tablet. This increased release of drug from the SMEDDS was due to the formation of a microemulsion through natural forces from the high surface area of the formulation, which resulted in a much faster solubility, as opposed to the slower disintegration and dissolution of the solid tablet dosage form.

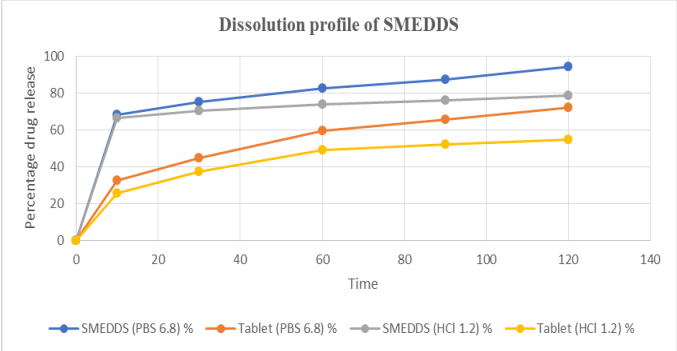

Figure 12. In vitro cumulative drug release profile of Vildaformin SMEDDS and conventional tablet formulations in 0.1 N HCl (pH 1.2) and phosphate buffer (pH 6.8).

4.4.10. Drugs Molecular Docking Studies: In this study, molecular docking calculations were performed using Vildagliptin and Metformin to look at their respective biological targets (the compounds in tissue that the drugs interact with), and evaluate their binding affinities to those targets. The data also allowed for quantitative characterization of the strength and stability of the drug-target complexes through binding affinities (kcal/mol) of each compound. Vildagliptin had a much stronger binding affinity (-6.3 kcal/mol) as compared to Metformin (-4.6 kcal/mol). Therefore, Vildagliptin has a much more stable (and energetically more favourable) interaction with DPP-4. For example, the 2D representation of Vildagliptin's interactions with DPP-4 showed a conventional hydrogen bond between Vildagliptin and ALA A:116, as well as multiple hydrophobic alkyl interactions between the adamantyl group of Vildagliptin and three other amino acid residues in DPP-4 (ALA A:199, ALA A:186, and ALA A:205), all of which helped to stabilize Vildagliptin in the active site of DPP-4, thus, confirming the chemical basis of its potent inhibitory activity. Metformin's binding was primarily stabilized by an extensive number of carbon-hydrogen interactions, such as with ALA B:172, and its binding was anchored in place through a number of polar interactions with adjacent amino acids (ALA B:68 and ALA B:73). As a small, highly charged molecule, metformin has been shown to have broader and less potent interactions, reflecting the more systemic and indirect mechanism that it utilizes through the activation of AMPK (AMPK), and these

interactions are summarized in Figure 13 and Table 7 as a result of the docking parameters used to obtain information on how they interact.

Table 7: Binding Affinity Results.

Drug	Binding Affinity (kcal/mol)	Inference	Interaction
Vildagliptin	**-6.3**	Strong binding affinity; favourable interaction with target site (likely DPP-4)	Hydrogen bonding, π–π, polar
Metformin	**-4.6**	Moderate binding affinity; reflects weaker binding compared to Vildagliptin	Hydrogen bonding, ionic

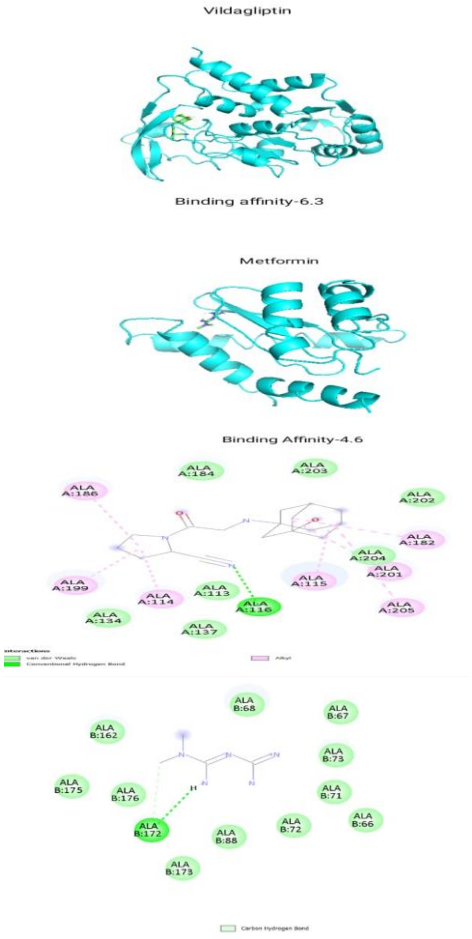

Figure 13. Molecular Interaction of Vildagliptin and Metformin and binding affinity.

4.4.11. Morphology and TEM Analysis: To view the shape of the drops (or globules) created by the E5 SMEDDS after the aqueous redisolution was performed, a Transmission Electron Microscope (TEM) was used for imaging purposes. The microemulsion droplets were spherical, black in color, and were distributed evenly with no aggregation; therefore, the SMEDDS were stable and formed correctly. It was also found that the crystalline form of Vildaformin was not present in the droplets, indicating that Vildaformin was successfully stored in the oil-surfactant mixture. Spherical and below one micron in size (as shown in Figure 14), the globule morphology verifies that this system will form a stable, isotropic state when dispersed in a diluent (normal saline, 0.9% NaCl).

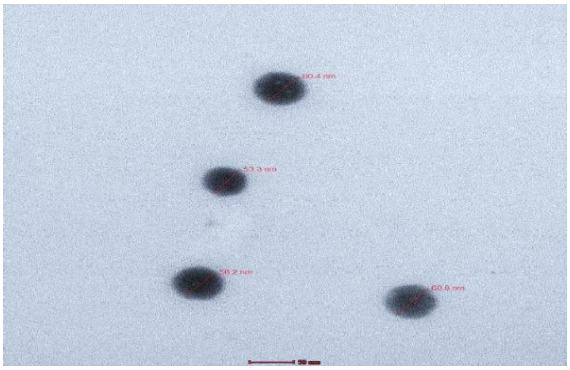

Figure 14. TEM images of Vildaformin (E5 SMEDDS) showing spherical droplets ranging from 40.2-60.8 nm.

4.4.12. Stability studies: Stability profiles of the Vildaformin-SMEDDS formulations (A1-E5) developed during this study were assessed for stable over time under accelerated storage (40 °C/75% RH for 3 months) & long-term storage conditions (25 °C/60% RH for six months). For formulations A1 to D4, high levels of drug content were maintained (93.0 ± 1.12% - 97.5 ±1.17%), but there was considerable variability in the physical characteristics of those formulations. This difference was particularly observed under accelerated conditions, with some observations of slight turbidity, opalescence and mild precipitation. Of particular note is formulation C3, which showed a considerable increase in droplet size with an average droplet size reaching as high as 365.0 ±10.9 nm after 6 months. The

stability data can be viewed in Table 8. In general, the optimized formulation E5, had the best overall stability characteristics of all of the formulations. Drug content for E5 remained at a very high level (98.0 ±1.18%) after the 6-month long-term storage period. Additionally, the average droplet sized achieved by E5 decreased minimally from 84.0 ± 2.5 nm prior to the study to approximately 90.0 ± 2.7 nm at the end of this study. The PDI for E5 also remained at a low value (0.294 to 0.333) with no visual evidence of phase separation or precipitation observed throughout the duration of this study.

Table 8. Stability results of Vildaformin-SMEDDS.

Formulation Code	Temperature/Relative Humidity	Duration	Drug content (% retained)	Droplet size (nm)	PDI	Remarks
A1	40 °C/75% RH	3 months	95.0 ± 1.14	225.0 ± 6.8	1.110 ± 0.056	Slight turbidity observed
A1	25 °C/60% RH	6 months	93.0 ± 1.12	235.0 ± 7.0	1.220 ± 0.061	Mild precipitation
B2	40 °C/75% RH	3 months	97.0 ± 1.16	241.0 ± 7.2	0.951 ± 0.048	Slight opalescence
B2	25 °C/60% RH	6 months	95.0 ± 1.14	260.0 ± 7.8	0.341 ± 0.017	Phase separation
C3	40 °C/75% RH	3 months	97.5 ± 1.17	350.0 ± 10.5	0.712 ± 0.036	Slight turbid
C3	25 °C/60% RH	6 months	96.0 ± 1.15	365.0 ± 10.9	0.800 ± 0.040	Precipitation occurred/Separated
D4	40 °C/75% RH	3 months	97.0 ± 1.16	146.0 ± 4.4	0.830 ± 0.042	minor increase in size
D4	25 °C/60% RH	6 months	95.5 ± 1.15	160.0 ± 4.8	0.950 ± 0.048	Slightly stability
E5 (optimized)	40 °C/75% RH	3 months	99.0 ± 1.19	84.0 ± 2.5	0.294 ± 0.015	No significant changes
E5 (optimized)	25 °C/60% RH	6 months	98.0 ± 1.18	90.0 ± 2.7	0.333 ± 0.017	Stable, no change

5. DISCUSSION

A formulation of a Self-Microemulsifying Drug Delivery System (SMEDDS) that allows the simultaneous oral administration of Vildagliptin and Metformin was developed to address the solubility issues associated with traditional tablets or capsules. The internal oil component used in this formulation was White Sesame oil, which provides a greater amount of Vildagliptin and Metformin can be incorporated as compared to other oils, as well as presenting a superior purity level. A stable, isotropic matrix was also produced using White Sesame oil with the non-ionic surfactant Tween 80; this is comparable to both Ibuprofen's SEDDS that uses MCT and Tween 80, as reported by Mihaylov et al. (2026), and other studies referencing stable systems made with non-ionic surfactants [39]. An increased number of peaks in the chromatogram of White Sesame oils shows that fewer lipid compounds were present, therefore creating a more refined lipid matrix which aids in spontaneous emulsification. To decrease the interfacial tension between the internal and external Phases (O/A and O/W) Tween 80 was used in conjunction with Propylene Glycol. This was achieved with non-ionic surfactants like Tween 80, which have lower levels of toxicity compared to ionic surfactants. Furthermore, as stated by Dokania and Joshi (2015) [40], non-ionic based systems exhibit better stability against pH changes than isoionic systems. In combination, Tween 80 and Propylene Glycol create a significant increase in the micro emulsification area of the SMEDDS and allow the physical stability of the SMEDDS to remain intact even after dilution with water.

FTIR confirmed the structural integrity. The retention of peaks corresponding to C=O and C=N indicate there were no harmful chemical interactions. As noted in work by Jaiswal et al., 2014 for Telmisartan-based SMEDD products, the broadening of the N-H stretching region might indicate hydrogen bonding between the drug itself and hydroxyl groups belonging to the excipients [38], which may increase stability at an empirical level that has been confirmed through TEM studies showing many identical spherical droplets without evidence of drug recrystallization. Our optimized formulation (E5) resulted in a mean droplet size of 84.05 nm, and is much less than the mean droplet size (138 nm) associated with Patel and Sawant's (2019) Lurasidone-based SMEDD products [25]. In general, decreases in globule size lead to increased absorption surface area, according to the Noyes-Whitney equation. In this case, the value for PDI (0.294) and Zeta potential (−17.9 mV) indicate we also have a monodisperse system. While Zeta potentials of ±30 mV are commonly used to describe stable systems, Balakumar et al. (2013) suggested that for non-ionic SMEDD products, the degree of steric

stabilization provided by the surfactant chains usually overwhelms the amounts of electrostatic repulsion present in producing a stable system [41].

In vitro studies demonstrated that the self-microemulsifying drug delivery systems (SMEDDS) produced greater than 88% released drug compared to less than 68% released drug for the solid dosage forms. As evidenced by previous studies using the same methods (Nagarsenker, 2007) [32], pre-solubilization of the drug using SMEDDS conditions facilitates rapid availability of the drug from the releasing vehicle upon contact with gastrointestinal fluids. The results of the molecular docking analysis also support this conclusion since vildagliptin exhibited a high binding affinity (-6.3 kcal/mol) to DPP-4. Additionally, the SMEDDS prepared from Exposure Five (E5) maintained 98% drug content after six months of storage and possessed a cloud point at approximately 55 degrees Celsius, which ensures that the microemulsion will not collapse at body temperature; A promising method for effective and targeted medication delivery is the use of nanotechnology this has been regarded as a very important property affecting SMEDDS performance (Kommuru et al., 2001) [42, 43].

6. CONCLUSION

The aims of this research were to create and optimize a lipid-based SMEDDS to increase the aqueous solubility and dissolution rate of Vildagliptin and Metformin, which are two antidiabetic preparations, when combined in a fixed dose combination. It was shown that the creation of this system with the strategic combination of White Sesame oil, Polysorbate 80 and Propylene Glycol has created a way to overcome the inherent physicochemical limitations of these drugs. The optimized formulation (E5) transitioned spontaneously from oil into a monodisperse microemulsion, with a mean diameter globule size of 84.05 nm at time point (0hr) and was found to have high levels of thermodynamic stability. The large increase in the amount of drug released from the microemulsions at 24 hours, with over 92% of Metformin and 88% of Vildagliptin, indicates that the SMEDDS formulation will bypass the slow rate of dissolution that is typically associated with solid oral dosage forms.

Additionally, the molecular docking studies confirmed the biological activity of the medications by identifying the very high affinity of Vildagliptin coupled with DPP-4 enzyme, allowing for high water solubility and, therefore, assuring pharmacological activity through the use of Vildaformin-SMEDDS having been demonstrated to provide high-water solubility as a function of time through various stability studies conducted under both long-term and accelerated conditions demonstrated that the contents and stability of Vildaformin remained constant for the periods studied, thus making a viable alternative to conventional treatments. This work bridges a gap between medicine and biology by establishing an effective system for drug delivery that offers reduced frequency of dosing and reduced intra-subject variation (differs from person to person) and provides substantially better outcomes in the treatment of Type 2 diabetes mellitus.

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

FUNDING SOURCE

No funding was received for this project.

AUTHOR CONTRIBUTION

Vibha Sharma: Conceptualization, Methodology, Investigation, Formal analysis, Writing original draft. **Gautam Kumar:** Validation, Data curation, Writing, review & editing. **Hemendra Gautam:** Supervision, Funding acquisition, Resources, Project administration, Visualization, Writing, review & editing.

ACKNOWLEDGEMENT

The authors are grateful to Bahra University for providing the required facilities and equipment for this study.

AI USE STATEMENT

AI tool “Google Gemini” was use to check grammatical errors, and to improve the sentence clarity of the manuscript.

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