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Formulation and Evaluation of Self Nanoemulsifying Drug Delivery System of Sitagliptin and Metformin

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Abstract:

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder requiring effective long-term glycemic control. Sitagliptin and Metformin Hydrochloride are widely used in combination therapy; however, both drugs exhibit limitations such as poor solubility and variable oral bioavailability, which can affect therapeutic efficacy. The present study aimed to develop and evaluate a liquid self-nanoemulsifying drug delivery system (SNEDDS) for the co-delivery of Sitagliptin and Metformin Hydrochloride to enhance their solubility, dissolution rate, and potential oral bioavailability. SNEDDS formulations were prepared using various combinations of oils, surfactants, and co-surfactants, followed by optimization based on emulsification efficiency, droplet size, polydispersity index (PDI), zeta potential, and drug content. Preformulation studies confirmed suitable excipients, with Garlic oil as the lipid phase and Cremophor EL and PEG 400 as effective surfactant and co-surfactant systems. The optimized formulations exhibited droplet sizes in the nanometric range (48–102 nm), acceptable PDI values, and zeta potential indicating moderate stability. Drug content analysis showed uniform incorporation of both drugs, and robustness to dilution confirmed formulation stability. In vitro diffusion studies demonstrated enhanced drug release, with cumulative release reaching up to 96.89% for Sitagliptin and 96.01% for Metformin over 12 hours. The results indicate that SNEDDS significantly improved the dissolution behavior of both drugs compared to conventional formulations. Overall, the developed SNEDDS presents a promising strategy for improving the oral delivery and therapeutic performance of Sitagliptin and Metformin Hydrochloride in T2DM management.

Keywords: Sitagliptin, Metformin, Self-Nanoemulsifying Drug Delivery System (SNEDDS), Droplet Size, Polydispersity Index, Zeta Potential, Solubility Enhancement, Cardiovascular Diseases, Oral Bioavailability, In Vitro Drug Release.

Introduction

Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by persistent hyperglycemia and requires long-term pharmacological management to maintain optimal glycemic control. Among the commonly prescribed antidiabetic agents, Sitagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, and Metformin Hydrochloride, a first-line biguanide, are widely used in combination therapy to achieve better therapeutic outcomes. However, both drugs exhibit certain physicochemical limitations, particularly related to poor aqueous solubility and variable oral bioavailability, which can significantly affect their therapeutic performance.[1-4]

To overcome these challenges, advanced drug delivery approaches are being explored. Among them, Self-Nanoemulsifying Drug Delivery Systems (SNEDDS) have gained considerable attention as a promising lipid-based formulation strategy. SNEDDS are isotropic mixtures of oils, surfactants, and co-surfactants that spontaneously form fine oil-in-water nanoemulsions upon mild agitation in gastrointestinal fluids. This results in enhanced drug dispersion, improved dissolution rate, and increased absorption, ultimately leading to better bioavailability of poorly soluble drugs.[5-7]

Despite the availability of conventional dosage forms and standard SNEDDS approaches, there is still a need for improved formulations that can effectively address issues such as solubility limitations, inconsistent absorption, and formulation instability.

In this context, developing a liquid SNEDDS for the combination of Sitagliptin and Metformin Hydrochloride offers a potential strategy to enhance their therapeutic efficiency while ensuring better patient compliance in T2DM management. [8-9] Therefore, the present study focuses on the design, development, and evaluation of liquid SNEDDS of Sitagliptin and Metformin Hydrochloride, with the aim of improving their solubility, dissolution behavior, and overall oral bioavailability through systematic formulation optimization and characterization.[10-12]

Materials and Methods

Materials

The study utilized Sitagliptin and Metformin as the active pharmaceutical ingredients (APIs). The excipients employed included Sorbitan Monostearate, Cremophor EL, Glycerol, Polyethylene Glycol 400 (PEG 400), and Garlic Oil. All chemicals and reagents were of analytical grade.

Equipment and Instruments

The following instruments were used in the study: analytical balance, digital pH meter, hot air oven, UV-visible spectrophotometer, Fourier-transform infrared (FTIR) spectrophotometer, and high-performance liquid chromatography (HPLC). Particle characterization was performed using a Zetasizer Nano (Model ZEN3600, Malvern, UK) for droplet size, polydispersity index (PDI), and zeta potential measurements.

Drug Evaluation

Prior to formulation, Sitagliptin and Metformin were evaluated for physicochemical properties. Organoleptic characteristics such as color, odor, and texture were recorded. Melting points were determined using a capillary tube and Thiele tube method.

Solubility studies were performed in various solvents to assess drug solubility. UV-visible spectroscopy was employed to determine the λmax of Sitagliptin (244 nm) and Metformin (226 nm). Infrared spectroscopy was conducted to confirm characteristic functional groups. Standard calibration

curves were prepared using serial dilutions and analyzed spectrophotometrically to quantify drug concentrations. [13-15]

Preformulation Studies

Preformulation studies were conducted to screen suitable oils, surfactants, and co-surfactants for solubility and emulsification efficiency.

The solubility of Sitagliptin and Metformin in different vehicles was assessed using the vial shake method. Emulsification studies were carried out by mixing surfactants and co-surfactants with selected oils, followed by dilution in water to evaluate the ease of emulsion formation, transparency, and phase stability.[16]

Preparation of SNEDDS

SNEDDS formulations were prepared using the specified ratios of oils, surfactants, co-surfactants, and drugs. Sitagliptin (10 mg) and Metformin (75 mg) were accurately weighed and dissolved in the selected oil.

Surfactants and co-surfactants were added to the oil-drug mixture, followed by heating at 40°C and sonication for 15 minutes to ensure uniform dispersion. The formulations were stored at room temperature until further evaluation. Ten formulations (F1–F10) were prepared with varying concentrations of excipients to optimize physicochemical properties.[17-18]

Table 1: Formulation Batches

Sr. No.	Ingredients (mg)	F1	F2	F3	F4	F5	F6	F7	F8	F9	F10
1.	Sitagliptin	10	10	10	10	10	10	10	10	10	10
2.	Metformin	75	75	75	75	75	75	75	75	75	75
3.	PEG	--	--	--	--	--	10	15	10	15	`10
4.	Glycerol	20	10	15	20	10	--	--	--	--	--
5.	Cremophor EL	60	70	50	60	70	--	--	--	--	--
6.	Sorbitianmonostearate	--	--	--	--	--	60	70	80	60	50
7.	Garlic Oil	5	10	10	10	10	--	--	--	--	--

Evaluation of Liquid SNEDDS [19-20]

1. **Visual Observation**: Formulations were diluted and observed at 37°C for 24 hours to detect phase separation or turbidity.
2. **Self-Emulsification Time**: One milliliter of SNEDDS was added to 100 mL distilled water at 37°C with gentle agitation (100 rpm). The time required for the formation of a clear or milky emulsion was recorded.
3. **Drug Content**: Formulations were diluted appropriately, and drug concentrations were determined using a UV-visible spectrophotometer based on previously prepared standard calibration curves.
4. **Robustness to Dilution**: Formulations were diluted to 10 mL, 50 mL, and 100 mL and monitored for 24 hours to detect phase separation or precipitation.
5. **Droplet Size, PDI, and Zeta Potential**: The droplet size, polydispersity index, and zeta potential of diluted SNEDDS formulations (1:1000 v/v in water) were measured using dynamic light scattering (DLS) via a Zetasizer Nano. Measurements were performed in triplicate to ensure reproducibility.
6. **In Vitro Diffusion Study**: Drug release from SNEDDS was evaluated using the dialysis membrane technique. One milliliter of SNEDDS, along with 0.5 mL of dialyzing medium, was placed inside a

dialysis membrane, which was then immersed in phosphate buffer (pH 1.2) under constant stirring at 100 rpm. Samples were withdrawn at predetermined time intervals, diluted appropriately, and analyzed spectrophotometrically. The withdrawn volume was replaced with fresh buffer to maintain sink conditions.

Results and Discussion

Analytical Evaluation

The organoleptic evaluation of Sitagliptin and Metformin revealed that both drugs were white crystalline powders with a bitter taste and were odorless. The observed melting points of Sitagliptin (120.3°C) and Metformin (224.1°C) were consistent with reported values, confirming the identity and purity of the APIs. Solubility studies indicated that Sitagliptin was soluble in water, soluble in ethanol and slightly soluble in pH 6.8 buffer, in pH 1.2 buffer, whereas Metformin was freely soluble in water, soluble in ethanol, soluble in pH 6.8 buffer, and freely soluble in pH 1.2 buffer. The UV-visible spectra of the drugs showed maximum absorbance at 244 nm for Sitagliptin and 226 nm for Metformin, which were used to construct standard calibration curves.

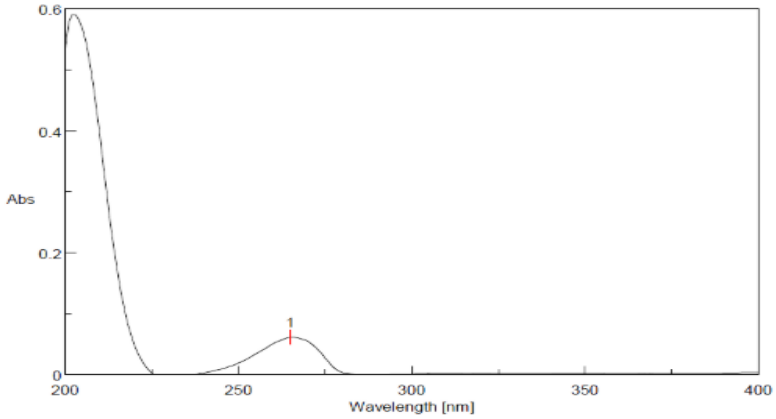

Figure 1: UV Spectra of Sitagliptin

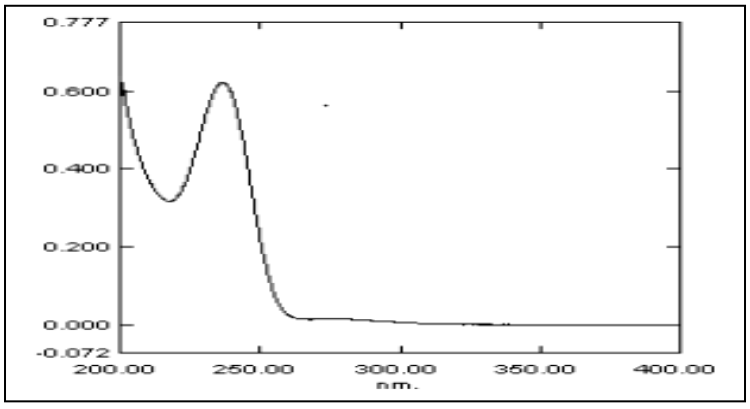

Figure 2: UV Spectra of Metformin

FTIR analysis confirmed the presence of characteristic functional groups of both drugs, showing no deviations from standard spectra, indicating the chemical integrity of the drugs.

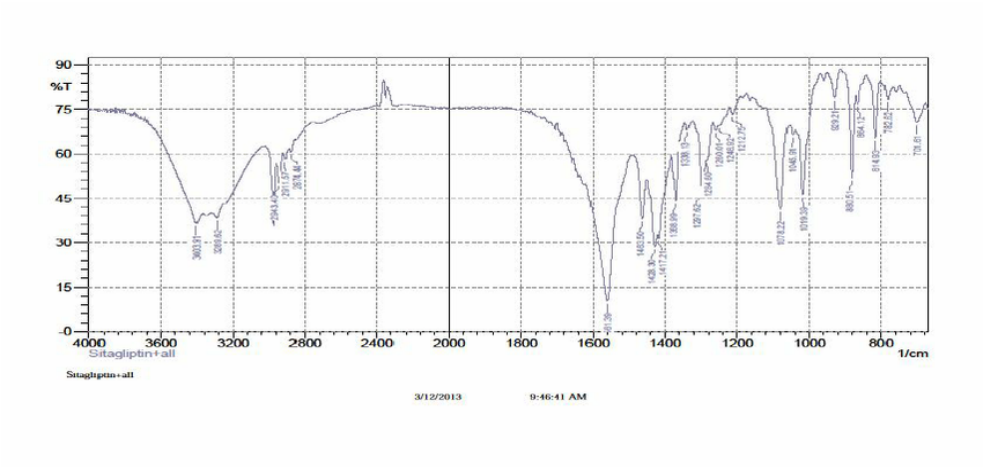

Figure 3: FTIR Spectrum of Sitagliptin

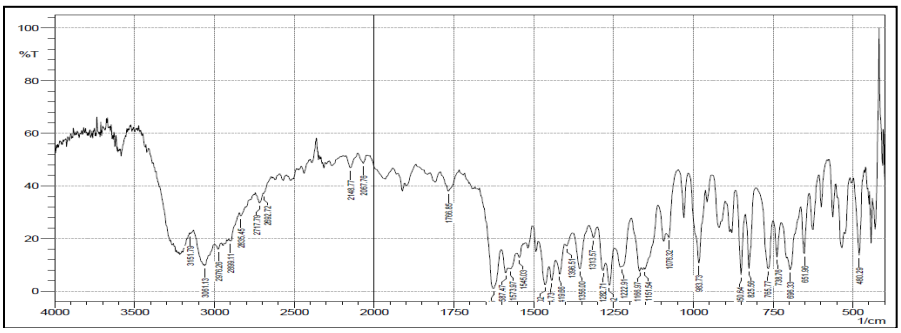

Figure 4: IR Spectra of Metformin

Preformulation Studies

Preformulation studies were conducted to identify suitable excipients for the SNEDDS formulation. Solubility studies in oils and surfactants revealed that Garlic oil demonstrated moderate solubilizing capacity for the drugs (87.62 mg/mL), while among the surfactants, PEG 400 showed the highest solubility (159.38 mg/mL) followed by Glycerol (84.35 mg/mL). These results highlighted the potential of Garlic oil as the lipid phase and PEG 400 as a co-surfactant to enhance drug solubility and stability in the formulation.

Emulsification studies indicated that Cremophor EL exhibited the highest percentage transparency (99.10%) and required the lowest number of inversions (5) to form a clear emulsion, demonstrating its superior emulsifying efficiency. PEG 400, although requiring more inversions (40), showed good transparency (96.48%), while Glycerol and Sorbitan monostearate showed moderate emulsification properties, suggesting that they may be more suitable as secondary surfactants.

Evaluation of Liquid SNEDDS

Drug content analysis of the prepared SNEDDS formulations (F1–F10) showed high uniformity, with Sitagliptin content ranging from 96.79% to 99.35% and Metformin content ranging from 91.62% to 96.77%, indicating accurate incorporation of the drugs into the formulations. The robustness to dilution study confirmed the stability of all formulations, as no phase separation or precipitation was observed upon dilution up to 100 mL.

Table 2: Evaluation of Liquid SNEDDS

Formulation	Sitagliptin Drug Content (%)	Metformin Drug Content (%)	Robustness to Dilution (10/50/100 mL)	Droplet Size (nm)	PDI	Zeta Potential (mV)
F1	97.24 ± 0.24	96.34 ± 0.742	Yes/Yes/Yes	48	0.32	-16.67
F2	96.79 ± 0.26	93.74 ± 0.457	Yes/Yes/Yes	90	0.62	-15.45
F3	98.67 ± 0.12	96.45 ± 1.134	Yes/Yes/Yes	85	0.55	-14.65
F4	98.86 ± 0.19	93.34 ± 1.771	Yes/Yes/Yes	70	0.57	-18.34
F5	99.15 ± 0.26	96.77 ± 0.347	Yes/Yes/Yes	53	0.51	-23.87
F6	99.10 ± 0.14	95.71 ± 0.128	Yes/Yes/Yes	52	0.47	-17.73
F7	98.36 ± 0.23	96.54 ± 0.346	Yes/Yes/Yes	102	0.76	-15.64
F8	98.31 ± 0.13	92.34 ± 0.712	Yes/Yes/Yes	93	0.53	-14.74
F9	99.35 ± 0.34	91.62 ± 0.744	Yes/Yes/Yes	74	0.48	-14.37
F10	99.10 ± 0.14	94.64 ± 0.224	Yes/Yes/Yes	55	0.44	-13.96

Droplet size analysis revealed particle sizes ranging from 48 nm to 102 nm, with polydispersity index (PDI) values between 0.32 and 0.76, indicating relatively uniform nanoemulsion formation.

Zeta potential measurements ranged from –13.96 mV to –23.87 mV, suggesting moderate stability of the dispersed droplets due to electrostatic repulsion.

The combination of small droplet size and favorable PDI is indicative of efficient self-emulsification and potential for enhanced drug absorption.

In Vitro Drug Release Studies: In vitro dissolution studies demonstrated a rapid and sustained release profile for both Sitagliptin and Metformin from the SNEDDS formulations. For Sitagliptin, cumulative drug release at 12 hours ranged from 91.46% to 96.89%, while Metformin release ranged from 92.55% to 96.01%.

Formulations F7, F9, and F10 showed relatively higher release rates, likely due to optimized excipient ratios promoting better emulsification and solubilization.

The dissolution profiles indicate that SNEDDS enhances the solubility and dissolution rate of both drugs, which can potentially improve oral bioavailability compared to conventional formulations.

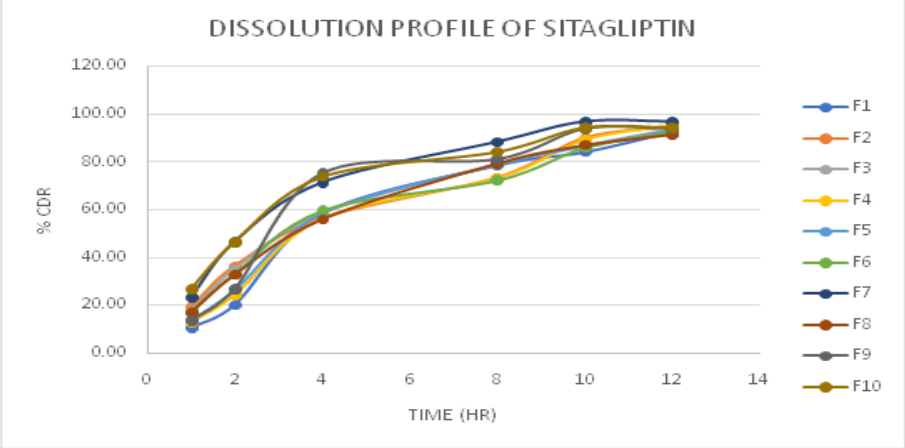

Figure 5: Dissolution Profile of Sitagliptin

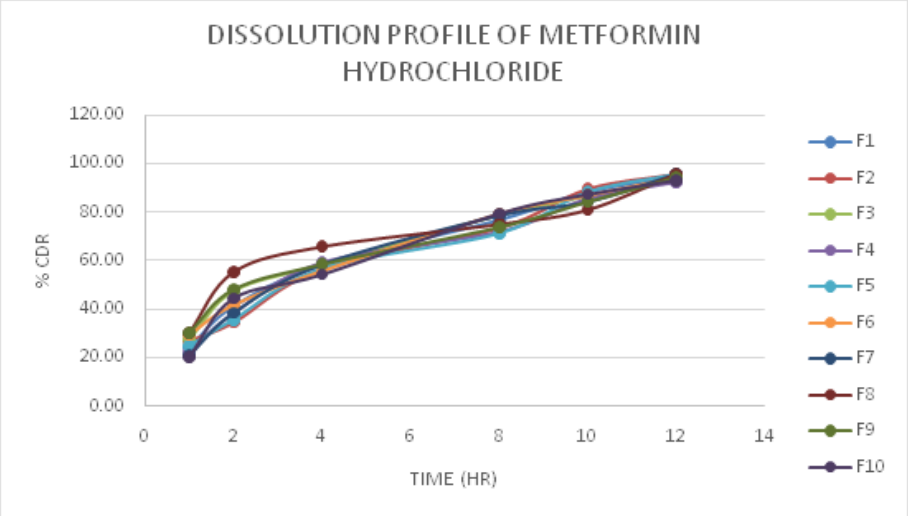

Figure 6: Dissolution Profile of Metformin

Overall, the analytical evaluation, preformulation studies, and evaluation of liquid SNEDDS demonstrated the successful development of a stable, compatible, and effective self-nanoemulsifying system for the co-delivery of Sitagliptin and Metformin. The combination of appropriate oils, surfactants, and co-surfactants resulted in nanoemulsions with favorable droplet size, PDI, zeta potential, and drug release characteristics, supporting the potential of SNEDDS to enhance solubility, stability, and bioavailability of poorly soluble drugs.

Conclusion

The present study successfully developed and evaluated self-nanoemulsifying drug delivery systems (SNEDDS) for the co-administration of Sitagliptin and Metformin, aiming to enhance the solubility, dissolution, and oral bioavailability of these poorly water-soluble drugs. Analytical evaluation confirmed the identity, purity, and physicochemical stability of the active pharmaceutical ingredients, while preformulation studies identified suitable oils, surfactants, and co-surfactants that provided optimal solubilization and emulsification properties. The prepared SNEDDS formulations exhibited uniform drug content, robust stability upon dilution, and efficient self-emulsification, as evidenced by favorable droplet size, polydispersity index (PDI), and zeta potential values. In vitro dissolution studies demonstrated rapid and sustained drug release, indicating enhanced solubilization and potential for improved oral absorption compared to conventional dosage forms.

Among the formulations, certain batches (F7, F9, and F10) displayed superior drug release, highlighting the importance of optimized excipient ratios in achieving effective nanoemulsion characteristics.

Overall, the study confirms that SNEDDS is a promising strategy for the co-delivery of Sitagliptin and Metformin, offering improved physicochemical stability, enhanced solubility, and controlled drug release. This approach has the potential to reduce dosing frequency, increase patient compliance, and improve therapeutic efficacy in the management of cardiovascular diseases.

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