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FORMULATION DEVELOPMENT AND EVALUATION OF SITAGLIPTIN-LOADED NANOSTRUCTURED LIPID CARRIERS FOR DIABETES MELLITUS

Anchal Sharma[1], Davinder Singh[1], Maninder Pal Singh[2], Ramica Sharma[3], Harleen Kaur[1]
[1]*Rayat Bahra Institute of Pharmacy, Village-Bohan, Hoshiarpur, 146001, Punjab, India.*
[2]*Corresponding Author, Rayat Bahra Institute of Pharmacy, Village-Bohan, Hoshiarpur, 146001, Punjab, India.*
[3] *University School of Pharmaceutical Sciences, Rayat Bahra University, Mohali, 140301 Punjab, India.*

Abstract: *Sitagliptin is dipeptidyl peptidase-4 (DPP-4) inhibitor which has extensive used for type 2 diabetes mellitus treatment by stimulating the level of incretion hormone to regulate glucose in the blood. The purpose of this research was to improve also evaluate nano lipid carriers (NLCs) of sitagliptin to increase its bioavailability, stability, also therapeutic potential of sitagliptin. Nine formulations (NLCs-F1 to NLCs-F9) were formulated using the hot homogenization technique using different concentrations of lipids. The characterization studies encompassed analysis of particle size, polydispersity index (PDI), zeta potential, drug entrapment efficiency, also in vitro drug release. NLCs-F4 and NLCs-F8, the optimally obtained, were of sizes 190nm and 351nm, correspondingly, and had PDI of 0.098 and 0.211, which indicated good mono dispersity. Entrapment efficiency was highest in NLCs-F4 (91.9±0.9) and NLCs-F8 (88.2±0.3). In vitro release studies of drug revealed biphasic release of drug with 82.49% and 80.46% drug release in 12 hours following Higuchi model drug release kinetics. From this study, it is evident that NLCs improve the bioavailability, stability, and controlled release of sitagliptin. The biocompatible lipidic drug delivery exhibits an easily scalable, solvent-free platform for pharma applications.*

Keywords: *NLCs, Sitagliptin, diabetes mellitus, bioavailability, drug loading, drug release*

INTRODUCTION

Sitagliptin is well-known inhibitor of dipeptidyl peptidase-4 (DPP-4) which is recommended for management based on individuals by type 2 diabetes. It prolongs action of incretin hormones {gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)}, by blocking their degradation [1]. When taken either by itself or in conjunction with other oral antidiabetic drugs, sitagliptin efficiently lowers fasting, postprandial, and HbA1c glucose levels. The event of hyperglycemia, it suppresses glucagon secretion and increases insulin secretion [2]. Sitagliptin phosphate possesses the chemical formula 7-[(3R)-3 amino-1-oxo-4 (2,4,5 Tri fluorophenyl) butyl]-5,6,7,8-tetrahydro-3-(trifluoromethyl)-1,2,4 triazolo [4,3-a] pyrazine phosphate (1:1) monohydrate. The molecular weight of the compound is 523.32 Da as well as its molecular formula is C16H15F6N5O·H3PO4·H2O [3].

A high blood sugar level is a hallmark of diabetes mellitus, a chronic metabolic disease. Diabetes is caused by the inability of the body either to synthesize a sufficient quantity of insulin or to utilize existing insulin properly[4, 5]. Insulin[6] is released from the pancreas into the bloodstream, where it facilitates cellular glucose uptake in insulin-sensitive tissues. Although it is usually difficult to define, which has a larger part to play, both decreased insulin release and defective tissue sensitivity to the action of insulin are reasons for impaired metabolism of carbohydrates, lipids, and proteins, and ultimately, insulin resistance resulting in hyperglycemia. [7, 8]. Urbanization and lifestyle changes are primary contributors to rising diabetes prevalence [5, 9]. The higher prevalence also has significant effects on healthcare costs globally, as diabetes carries the threat of both acute complications and chronic complications (retinopathy, nephropathy, and neuropathy). Uncontrolled diabetes can cause life-threatening situations like diabetic ketoacidosis (primarily in type 1 diabetes) [10, 11] or hyperosmolar hyperglycemic state (in type 2 diabetes)[12, 13]. The increasing prevalence of diabetes emphasizes the need for better prevention and control measures across the globe [4, 14].

Sitagliptin is dipeptidyl peptidase-4 (DPP-4) inhibitor that raises the concentrations of incretin hormones, namely glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP). These hormones play an important role in controlling blood glucose levels through the stimulation of insulin release also inhibition of glucagon secretion in glucose-dependent method. This activity leads to improved glycemic control in affected role with type 2 diabetes mellitus (T2DM). Sitagliptin is usually given as add-on to exercise and diet for lowering blood sugar in adults with T2DM [15-17]. It is prescribed by means of monotherapy or with other antidiabetic medications such as metformin, thiazolidinediones, sulfonylureas, or insulin when monotherapy does not attain sufficient glycemic control. It is not indicated for type 1 diabetes or in patients with a history of pancreatitis. With regard to effectiveness, Sitagliptin was found to lower HbA1c levels by 0.5% to 1.1%, both when used as monotherapy and when combined with other medications. Sitagliptin reduces fasting plasma glucose and postprandial glucose safely, allowing patients to meet their glycemic goal. Sitagliptin is tolerable and has a safety profile equivalent to placebo according to clinical trials[17, 18]. Minimal chance of hypoglycemia, especially if not combined with hypoglycemia-inducing drugs like sulfonylureas. Sitagliptin is also weight-neutral, hence it is a choice of first option among patients who are weight-conscious. While there are no serious adverse reactions, some have experienced mild gastrointestinal distress and slight increases in serum creatinine levels. Sitagliptin is also safe and effective in elderly patients with type 2 diabetes and offers significant glycemic control with minimal side effects. However, for affected role by renal impairment that is moderate to severe, adjustments in dosing are advisable to maintain safety and effectiveness[19].

Solid particles or particulate dispersions with sizes between 10 and 1000nm are referred to as nanoparticles [20]. A nanoparticle matrix contains the medicine either dissolved, entrapped, encapsulated, or attached. Nanoscale particles play a vital role in modern medicine, especially in drug delivery, by enhancing solubility, stability, and precise targeting of drugs to specific tissues or cells [21]. Their tiny size enables them to cross biological barriers and deliver therapeutic agents, like drugs, proteins, or genes, directly to the action site, boosting effectiveness and reducing side effects. Made from materials such as polymers and lipids, nanoparticles can carry or bind active ingredients, altering pharmacokinetics and pharmacodynamics to improve overall treatment outcomes. Moreover, target ligands may be bound onto nanoparticle surfaces or used along with magnetic guidance for site-directed targeting. This flexible system is deliverable by multiple ways, like oral, nasal, parenteral, also intraocular delivery, thus being very versatile for various therapeutic uses [22, 23].

Nanostructured lipid carriers (NLCs), a lipid-based drug delivery system of nanoparticles, engineered for encapsulation and delivery of active pharmaceutical agents [24, 25]. Their structure is more stable and flexible than that of traditional lipid nanoparticles because liquid lipids are additional to a solid lipid matrix to produce them. NLCs offer improved drug encapsulation efficiency, tailored therapeutic agent administration, controlled release profiles, and enhanced bioavailability. Oral, topical, transdermal, ocular, and parenteral methods can all be used to deliver nano-based systems. NLCs stay solid even at room temperature and are organized via combining solid lipids and liquid lipids [26, 27]. Its advantages include biocompatible lipids, controlled drug release from carrier, ability to produce drugs on huge measure consuming current technology, avoidance of first-pass metabolism, also drug protection against biochemical degradation. NLCs, larger lipid ratios (up to 95%) can be utilized [28, 29].

In the present work, we synthesized sitagliptin-loaded nanostructured lipid carriers for diabetes mellitus. The proposed work is designed to improve the bioavailability and hypoglycemic activity of sitagliptin by incorporating the drug into nanostructured lipid carriers. The NLCs were characterized using UV spectroscopy, FTIR, zeta sizer, and transmission electron microscopy. After characterization, sitagliptin was

successfully loaded onto the NLCs. This work addresses both the solubility and systemic absorption challenges associated with sitagliptin.

MATERIAL AND METHODOLOGY:

Material used in NLCs:

Sitagliptin was procured from Life Care, located at 70/1 Dharampur Sai Road, Himachal Pradesh; stearic acid also Tween 80 were obtained commencing CDH Central Drug House (P) Ltd., New Delhi; castor oil and almond oil were sourced from Yash Exports Pvt. Ltd., Rajasthan; and distilled water prepared in-house.

Preparation of NLCs

Hot homogenization process is utilized for preparation of NLCs. This approach involves homogenization at a high temperature. Solid lipids melt at higher temperature, i.e., 5–10 degrees Celsius above their melting point. Dispersion is produced by mixing the medication to be encapsulated with liquid fat. To create a pre-emulsion, this combination is then liquified in an aqueous surfactant solution that has already been heated to equal temperature and put on a high-shear mixing equipment. The resulting pre-emulsion is further subjected for homogenization at 3000 rpm for 30 minutes. Nanoparticles are produced when the lipid recrystallizes in the cooling nano emulsions [30-32]. Formula for different formulation is shown in table no 1.

Table no 1. Formulation of NLCs

Formulation	Drug (in grams)	Solid Lipid Stearic acid (in grams)	Liquid Lipid Almond oil (in grams)	Liquid Lipid Castor Oil (in grams)	Surfactant Tween 80 (in %)
F1	10	0.9	0.1	~~~	2.5
F2	10	0.8	0.2	~~~	2.5
F3	10	0.7	0.3	~~~	2.5
F4	10	0.6	0.4	~~~	2.5
F5	10	0.9	~~~	0.1	2.5
F6	10	0.8	~~~	0.2	2.5
F7	10	0.7	~~~	0.3	2.5
F8	10	0.6	~~~	0.4	2.5
F9	10	0.5	~~~	0.5	2.5

Characterization of NLCs

The optical characteristics were measured using a UV-Visible spectrophotometer (Systolic 2201). FTIR spectra, ranging from 400 to 4000 cm^{-1}, were recorded using a PerkinElmer Spectrum 2 instrument. Particle size, poly disparity index (PDI), also zeta potential was analyzed with Malvern Zeta sizer. Transmission electron microscopy (TEM) pictures were acquired with HRTEM 2100 Plus (JEOL, Japan).

Entrapment efficiency

By centrifuging a predetermined volume of NLC dispersion and analyzing the supernatant, concentration of medicine in dispersion media is ascertained. After centrifugation, the free medicine shall be remained in the supernatant and form NLC sediment. To find the concentration of entrapped drug, subtract concentration of free drug from early concentration of drug in dispersion. Drug escape from matrix in

media is decreased and entrapment efficiency is increased when a drug is more soluble in a lipid blend [33, 34].

% EE= $\frac{Ic-Fc}{Ic} \times 100$

EE= Entrapment efficiency
Ic= Initial concentration of drug in dispersion
Fc= Concentration of drug in supernatant

In-vitro drug release

Here's a rephrased, plagiarism-free version of your paragraph while retaining the technical accuracy and scientific context:

In vitro Drug Release Study of Sitagliptin Nano formulation

In vitro release of Sitagliptin from the organized Nano formulations evaluated using the membrane diffusion method. A precise quantity of the formulation, corresponding to 10 mg of Sitagliptin, was placed into a diffusion cell with a diameter of 2.5 cm. One end of cell was sealed with a dialysis membrane. Cell was then immersed in a dissolution vessel containing 90 mL of phosphate buffer (pH 7.4), maintained at continual temperature of 37 ± 0.5°C. The setup was rotated continuously at 50 rpm to ensure unbroken mixing. At predetermined time intervals, samples were withdrawn from the medium and replaced with an equal volume of fresh phosphate buffer to maintain sink conditions. Collected trials were examined by UV-visible spectrophotometer at 312 nm. The resulting drug release data were further analyzed using various kinetic models to determine the release mechanism [35-37].

Stability studies

The most promising formulation from nanostructured lipid carriers (NLCs), chosen based on its physicochemical characterization, entrapment efficiency, also *in vitro* drug release profile, was imperilled to stability testing over a period of one month. The objective of this study was to assess the influence of various environmental factors—such as temperature, humidity, and light—on the quality and performance of the formulation over time. This evaluation aids in determining appropriate storage conditions, retest intervals, and shelf life. In accordance with ICH guidelines, the selected formulations were sealed in glass vials also stored at 4°C and at 27°C with 75% relative humidity (RH). Samples were withdrawn at defined intervals—after 1 day, 1 week, and 1 month—and assessed for physical characteristics including clarity, visual appearance, and drug release behavior [38, 39].

RESULT AND DISCUSSION

Optical Properties

Sitagliptin phosphate was freely soluble in water but slightly soluble in chloroform and acetone. The melting point ranged from 215.60°C to 216.70°C. Partition coefficient (log P) of sitagliptin appeared to be 1.556, indicating moderate lipophilicity. A calibration curve for sitagliptin was ready in phosphate buffer at pH 7.4 to determine calibration equation for linearity curve, with an r^2 value of 0.9993, confirming excellent linearity, as shown in Figure 1.

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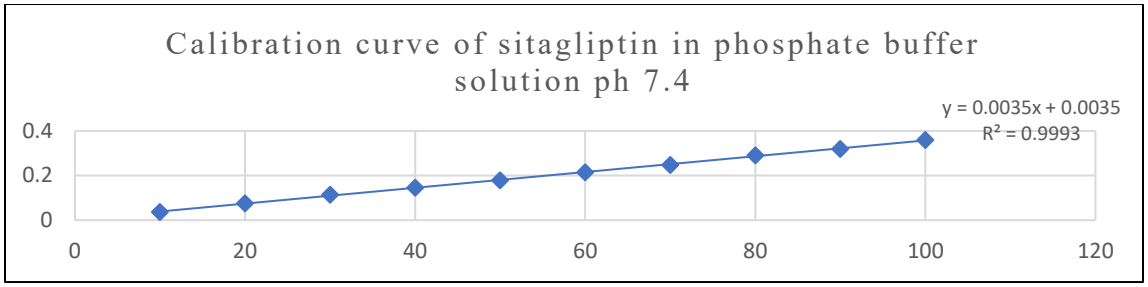

Figure 1: Calibration curve of Sitagliptin in phosphate buffer solution pH 7.4

Fourier Transform Infra-Red Spectroscopy (FTIR)

FTIR spectrum of Sitagliptin was concordant with functional group present in structure of Sitagliptin, Table No. 1, which shows the frequency of detected bands plus their interpretation. Bands obtained for (CH_3) group at 3059.0cm^{-1}(3000-3200cm^{-1}), for (C-H)group at 2901.44(2800-2900cm^{-1}), for (C=C) group at 1669.29(1625-1440cm^{-1}), for (NO_2) group at 1514.10 (1490-1570cm^{-1}), for (C-F) group at 661.15 (650-750cm^{-1}), for (C-O) group at (1100.0-1250.8cm^{-1}), for (C-OH) group at (1000-1400cm^{-1}) obtained which is shown in figure 2. The purity of the procured sample was confirmed by its FTIR Spectrum.

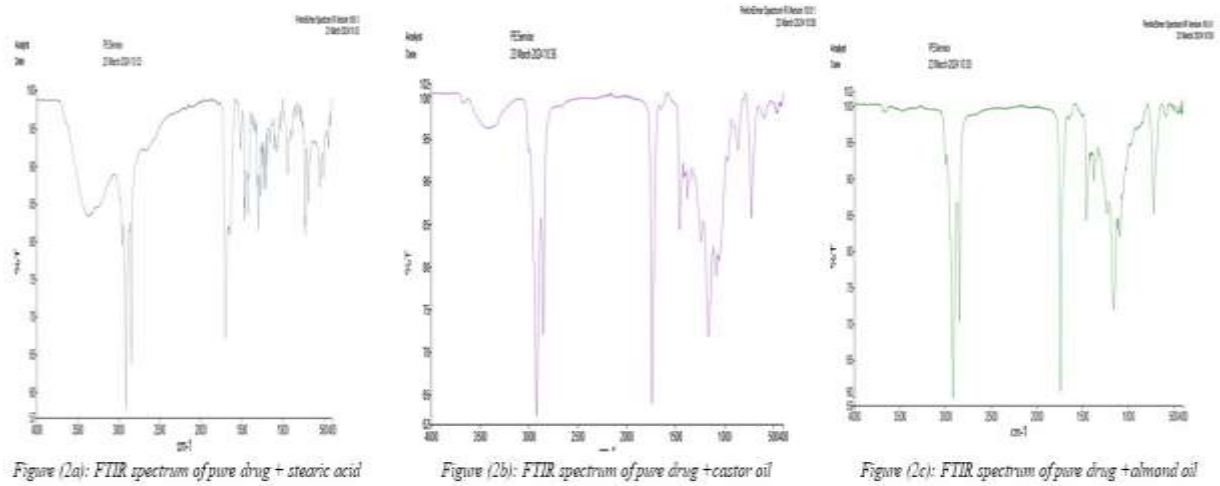

Figure 2: FTIR Spectrum of Pure drug with stearic acid, castor oil, and almond oil

Particle Size Analysis:

Particle size analysis was used to characterize the formulations. Every formulation fell within the range of nanometers. The diameter of the entire formulation was found to be in the range of 130 to 250nm in the case of NLCs. When the ratio of lipids increases and insufficient surfactant is present to cover the lipid droplets' surface, it leads to increase in particle size. When the amount of liquid lipids is greater than before, overall particle size decreases. With escalation in concentration of the liquid lipid, particle size decreases, based on fact that lower viscosity of lipophilic phase results in decreased particle size. Table no 2 shows the particle size of various formulations.

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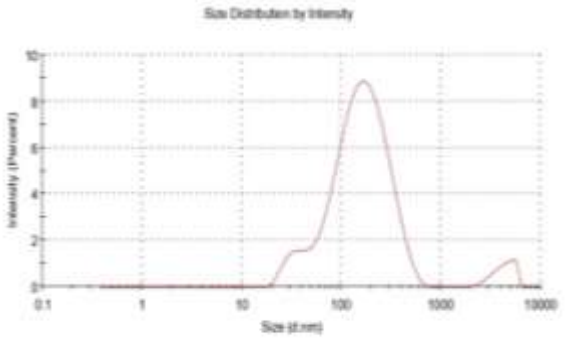

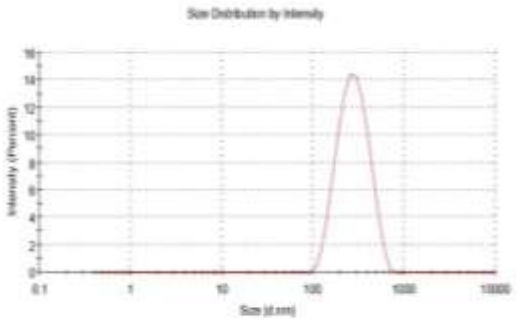

Figure 3: Particle size of formulation

Poly-Dispersity Index (PDI)

It was observed that the PDI was found to be un-modeled, with PDI ranging from 0.098 to 0.320 for all formulations. Best formulations were F4 (0.098) also F8 (0.211), which are shown in Table 2.

Table no 2: shows particle size, PDI, zeta potential, and % entrapment efficiency of different formulations of NLCs.

Sr no.	**Formulations**	**Particle size**	**PDI**	**Zeta Potential(mV)**	**% Entrapment Efficiency**
1	NLCs 1	0.221±0.025	0.213	-12.7	90.50±0.4
2	NLCs 2	0.143±0.058	0.351	-12.1	88.82±1.3
3	NLCs 3	0.191±0.024	0.218	-11.1	89.9±0.3
4	**NLCs 4**	**0.379±0.002**	**0.098**	**-8.65**	**91.9±0.9**
5	NLCs 5	0.19±0.037	0.227	-12.7	87.6±0.2
6	NLCs 6	0.223±0.028	0.193	-11.3	91.0±0.4
7	NLCs 7	0.433±0.031	0.320	-22.22	90.8±0.8
8	**NLCs 8**	**0.155±0.052**	**0.211**	**-11.3**	**88.2±0.3**
9	NLCs 9	0.195±0.085	0.266	-12.2	85.1±0.4

Zeta potential

Zeta potential, which reflects surface charge of particles, plays a significant role in determining the stability of colloidal systems by influencing electrostatic repulsion between particles. Formulations F1 through F9 were chosen for zeta potential evaluation based on their particle size distribution also entrapment efficiency. The measured zeta potential values for these formulations were as follows: F1 (-12.7 mV), F2 (-12.1 mV), F3 (-11.1 mV), F4 (-8.65 mV), F5 (-12.7 mV), F6 (-11.3 mV), F7 (-22.2 mV), F8 (-11.3 mV), and F9 (-12.2 mV). So, the zeta potential results are the best formulation shown in Figure 4, and values are shown in Table 2.

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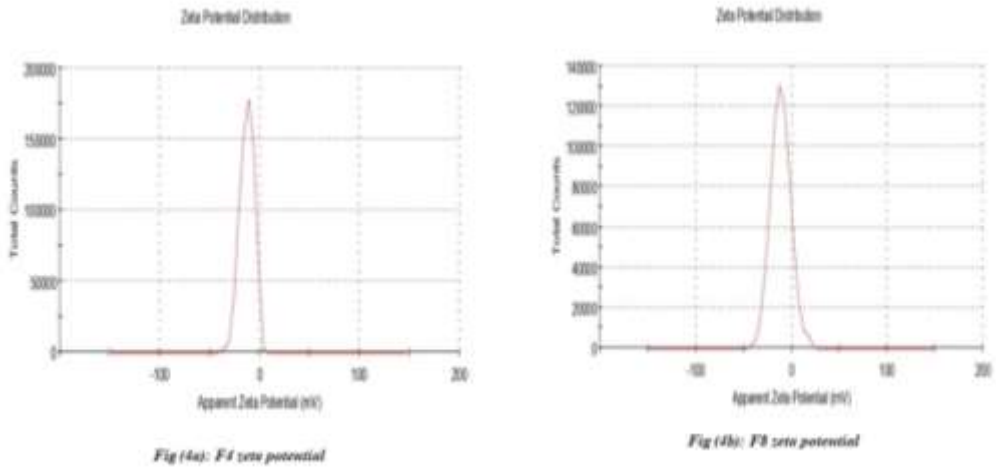

Figure 4: Zeta potential of the formulation

Percentage Entrapment Efficiency:
The sitagliptin-loaded NLC formulations' entrapment efficiency was analyzed using UV spectroscopy. All the formulations showed entrapment efficiency in the range of 85.1±0.4 to 91.9±0.3. The highest entrapment efficiency of 91.9±0.9 was observed in NLC. % Entrapment efficiency values of different formulations are shown in Table 2.

***In-vitro* release study:**
The release profile of Sitagliptin from the developed formulation was assessed using the membrane diffusion method. A custom in vitro diffusion setup was constructed, utilizing a dialysis membrane as the semi-permeable barrier. This setup consisted of glass test tube open at equally ends, with one end sealed using a pre-soaked dialysis membrane (molecular weight cut-off: 10,000–12,000 Da) and the opposite end used for introducing the formulation. A precisely measured quantity of the formulation equivalent to 5 mg of Sitagliptin was placed into test tube, which had a diameter of 2.5 cm.

The diffusion cell was immersed in dissolution vessel containing 50 mL of phosphate buffer, with temperature maintained at 37 ± 0.5 °C. System was stirred at constant speed of 50 rpm to ensure uniform diffusion. At hourly intervals, samples were withdrawn from the release medium and immediately replaced with an equal volume of fresh buffer to maintain sink conditions. The collected samples were analyzed using a visible spectrophotometer at 232 nm, using a buffer solution as the blank. All measurements were conducted in triplicate to ensure reproducibility.

In best formulation, NLC took 12 hours to release 82.49% of the drug. The release of up to 56.8% of the drug was at 8 hours in the formulation study. This indicates that 50% of the drug Release was completed in the first 8 hours of the formulation study. Figure 5 shows graphical

Representation of *in vitro* cumulative drug release of NLCs of the formulation.

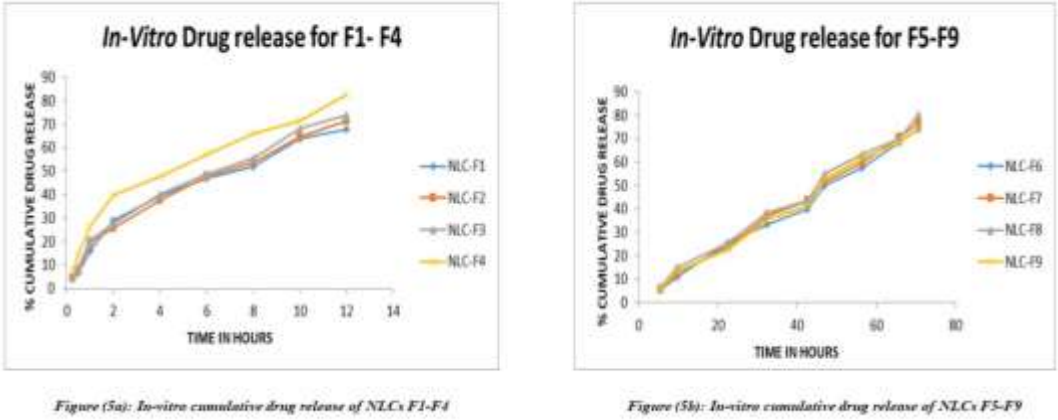

Figure (5a): In-vitro cumulative drug release of NLCs F1-F4 *Figure (5b): In-vitro cumulative drug release of NLCs F5-F9*

Figure 5: *In vitro* cumulative drug release of NLCs of Formulation

Drug release kinetics

In vitro drug release data, release kinetics were calculated, which are shown in Table 3. r^2 value confirms that formulations follow the Higuchi model, resulting in a diffusion-controlled drug release mechanism.

Table No. 3: *In-vitro* release models for Sitagliptin for NLCs best formulations (F4 and F8)

KINETIC MODELS	F4 FORMULATION		F8 FORMULATION	
	r^2	n^2	r^2	n^2
Zero Order	0.9125	5.7629	0.92	5.6381
First Order	0.939	-5.7821	0.9368	-5.751
Higuchi Model	0.9849	23.48	0.9842	22.87
Korsemyer-Peppas Model	0.96654	0.5688	0.9568	0.5774
Hixson Crowell Model	0.8126	0.4521	0.8203	0.4522

Transmission Electron Microscopy (TEM)

The microstructure scale of sitagliptin-loaded NLCs was characterized using TEM. After being properly diluted with distilled water and put on the carbon-coated copper grid, NLCs were sonicated for two minutes. Formulations were studied below transmission electron microscope operating at 200 kV. Figure 6 shows the TEM images of optimized NLC formulations F4 and F8.

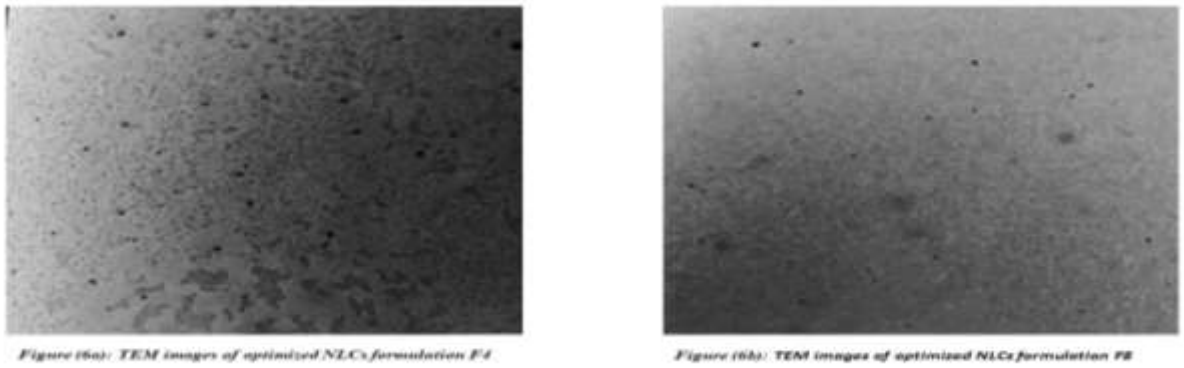

Figure 6: TEM images of optimized NLCs formulation (f4 and f8)

Stability studies

Selected best preparation from NLCs, grounded on characterization, entrapment efficiency also in-vitro release reading was selection and subjected to stability studies for one month. Formulations were withdrawn after 1 day, 1 week also 1 month and analysed for physical characterization such as appearance, percentage entrapment efficiency, also drug release profile. Values of different parameters are shown in Tables 4 and 5, indicate minor changes in the formulation occur due to storage conditions.

Table No. 4: stability studies result of NLCs formulation (F4 and F8)

Time of storage	4˚C			37℃±75% Rh		
	Colour	Drug release	% EE	Colour	Drug release	% EE
Zero day	No change in colour	82.49±0.01	91.9±0.9	No change in colour	82.49±0.01	91.9±0.9
One day	No change in colour	82.20±1.33	91.2±1.87	No change in colour	81.25±1.25	89.27±0.11
One week	No change in colour	81.89±0.75	90.1±0.22	No change in colour	79.29±1.29	87.5±0.97
One month	No change in colour	81.45±1.54	89.1±1.08	No change in colour	76.76±1.35	85.68±0.76

Table No. 5: stability studies result of NLCs formulation (F4 and F8)

Time of storage	4˚C			37℃±75% Rh		
	Colour	Drug release	% EE	Colour	Drug release	% EE
Zero day	No change in colour	80.46±0.55	88.2±0.3	No change in colour	80.46±0.55	88.2±0.3
One day	No change in colour	79.79±1.33	87.1±1.87	No change in colour	79.59±1.33	86.27±0.11
One week	No change in colour	78.89±0.75	86.7±0.22	No change in colour	77.89±0.75	83.51±0.97

One month	No change in colour	77.15±1.54	85.4±1.08	No change in colour	75.45±1.54	81.68±0.76

CONCLUSION

Nine Nano lipid carrier (NLCs) formulations (NLCs-F1 to NLCs-F9) were developed with varying lipid concentrations. Several evaluations were conducted to determine the best formulations, including particle size, poly dispersity index (PDI), entrapment efficiency, in vitro drug release, also drug release kinetics. The particle sizes were between 190-433 nm, and the NLCs-F4 (0.19 nm) and NLCs-F8 (0.351 nm) were the optimal ones. Their PDI values of 0.098 for NLCs-F4 and 0.211 for NLCs-F8 reflected good uniformity. Entrapment efficiency was greatest in NLCs-F4 (91.9±0.9) and NLCs-F8 (88.2±0.3). Drug release studies revealed an 82.49±0.23% and 80.46±0.39% release, where NLCs-F4 and NLCs-F8 displayed biphasic release. Kinetic experiments confirmed the Higuchi model of drug release. NLCs formulation-enhanced preparations enhance the bioavailability, stability, and prolonged release of sitagliptin, leading to effective control of blood glucose and reduced side effects in diabetes patients. NLCs with their solid and liquid lipid composition give protection to the drug and prolonged release. Their preparation is based on the use of FDA-approved biocompatible lipids and surfactants for oral delivery. It is a solvent-free, scale-up, and versatile process commonly used in pharmaceutical and cosmetic manufacturing. Ongoing advancements in NLCs technology help deliver enhanced drug delivery systems, which are key to more efficient diabetes treatment. More research and trials are needed to confirm these benefits in full.

FUNDING

No funding was received to support this study.

ETHICS DECLARATION

Not applicable.

CONFLICT OF INTEREST

Authors declare no conflict of interest, financial or otherwise.

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