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A Direct Compression Immediate-Release Triple-Drug Antidiabetic Tablet Including Metformin HCl, Sitagliptin Phosphate, and Glipizide: Formulation, Optimization, Evaluation and Stability-Indicating RP-HPLC Method Validation

Komal N Gupta[1], Pavankumar D. Chopade[2]

Oriental college of pharmacy Sanpada Navi Mumbai, India.

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ABSTRACT

A reverse-phase high-performance liquid chromatographic (RP-HPLC) method was developed and validated for the simultaneous determination of Metformin HCL, Sitagliptin phosphate, & Glipizide within active pharmaceutical ingredients (APIs) and in a fixed-dose immediate-release tablet formulation. The chromatographic separation was accomplished using a mobile phase of methanol, acetonitrile, and phosphate buffer (35:20:45 v/v/v, pH 3.0), using UV detection at 230 nm. The validation was done according to the ICH Q2(R1) guidelines, demonstrating adequate linearity, accuracy, precision, and specificity. The method was found to be linear in relation to formulation strengths, with LOD and LOQ values of 37.03 and 112.2 µg/ml for Metformin HCL, 5.2 and 15.77 µg/ml for Sitagliptin phosphate, and 0.55 and 1.67 µg/ml for Glipizide, respectively. An immediate-release tablet formulation is developed by the direct compression method using sodium starch glycolate as a superdisintegrant, microcrystalline cellulose as a binder, lactose anhydrous as a diluent, and talc and magnesium stearate as glidants and lubricants. The tablets were steered for pre-compression and post-compression parameters, which fulfilled the compendial specifications. The results of dissolution studies indicated that 73% of the total drug content was released within 30 minutes, which confirmed their immediate-release profile. The accelerated and intermediate stability studies at 30°C/70% RH and 25°C/60% RH indicated the stability of the optimized formulation, which was supported by the developed RP-HPLC method for regular examination and quality control of the fixed-dose combination, proving it applicable in industries.

Keywords : RP-HPLC, Method Validation, Forced degradation, Immediate-release (IR) tablet, Direct compression (DC), Fixed dose combination (FDC)

ABBREVIATIONS

IR - Immediate-release

DC – Direct compression

IP – Indian pharmacopeia

RP-HPLC – Reverse phase high performance liquid chromatography

INTRODUCTION

Metformin HCL is a biguanide, an oral antihyperglycemic agent commonly used for the treatment of type 2 diabetes. A popular antidiabetic medication is metformin HCL, a white, crystalline powder. 3-(diaminomethylidene)-1,1-dimethylguanidine hydrochloride is its IUPAC designation. It is a chemical with the molecular weight of 165.62 g/mol and the molecular formula $C_4H_{11}N_5 \cdot HCl$. It exhibits good thermal stability with a melting point between 223 and 226°C. Class III, which is highly soluble but weakly permeable, is where metformin HCL is classified according to the Biopharmaceutics Classification System (BCS). It is a perfect topic for immediate-release formulations because of these properties, which define its composition and absorption profile. (1) It improves insulin sensitivity by better peripheral glucose uptake and utilization, lowers intestinal glucose absorption, and decreases hepatic glucose synthesis. It works by activating the AMP-activated protein kinase (AMPK), an essential liver enzyme that controls insulin signaling, energy balance throughout the body, and the metabolism of fats and carbohydrates. The inhibitory effect of metformin HCL on hepatic glucose production, which improves glycemic control, depends on AMPK activation. (2,3)

Sitagliptin phosphate is an oral antidiabetic agent, belonging to the dipeptidyl peptidase-4 (DPP-4) inhibitor class, used in the treatment of type 2 diabetes. Sitagliptin phosphate is a white crystalline powder with the application as an oral antihyperglycemic medication. Its IUPAC name is (3R)-3-amino-1-[3-(trifluoromethyl)-6,8-dihydro-5H-[1,2,4]triazolo[4,3-a]pyrazin-7-yl]-4-(2,4,5-trifluorophenyl)butan-1-one; phosphoric acid. The molecular formula for the drug is $C_{16}H_{15}F_6N_5O \cdot H_3PO_4$, while the molecular weight is 505.31 g/mol. It has a melting point of about 206°C, indicating good thermal stability. According to the Biopharmaceutics Classification System (BCS), sitagliptin phosphate belongs to Class III compound, it's means high solubility and low permeability, with associated implications for its absorption behavior and formulation approach. (4,5) Sitagliptin phosphate works by effectively inhibiting the DPP-4 enzyme, which breaks down incretin hormones such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).Through inhibition of incretin inactivation, sitagliptin phosphate increases insulin secretion and inhibits glucagon release from the pancreas, thus achieving improved glycemic control as well as maintaining normal blood glucose levels. (2,6)

Glipizide is a second-generation sulfonylurea and is prescribed to reduce blood glucose concentrations in type 2 diabetes mellitus patients. Glipizide is a white, crystalline powder. Its IUPAC designation is N-[2-[4-(cyclohexylcarbamoylsulfamoyl)phenyl]ethyl]-5-methylpyrazine-2-carboxamide. The molecular formula of the compound is $C_{21}H_{27}N_5O_4S$, and its molecular weight is 445.5 g/mol. It has a melting point of 208–209°C, indicating its heat stability. Based on the Biopharmaceutics Classification System (BCS), Glipizide is classified under Class II, which exhibits low solubility and high permeability. This classification is a reflection of the need for formulation strategies that enhance its rate of dissolution for improved oral bioavailability. (7) It mainly functions by inducing insulin secretion from the pancreatic β-cells through inhibition of ATP-sensitive potassium (K+) channels. Inhibition decreases the potassium conductance, causing membrane depolarization and the resultant opening of voltage-sensitive calcium (Ca2+) channels. The subsequent influx of calcium ions raises intracellular calcium, thereby triggering exocytosis to release insulin. Glipizide also decreases hepatic glucose production to add to enhanced blood glucose control. (3)

The fixed dose combination of metformin HCL, sitagliptin phosphate, and glimepiride is typically indicated for the tretment of Type 2 Diabetes Mellitus (T2DM), best exemplified by the commercially available formulation Istamet G-IR. While this combination appears to achieve good glycemic control, glimepiride presents certain limitations in this combination. Glimepiride is a potent sulfonylurea that increases the risk of hypoglycemia, weight gain, and negative cardiovascular consequences in older adults, those who are overweight, and those who have comorbid conditions. Unwanted effects such as these compromise the safety of the patient, diminish the prospects for compliance, and impair long-term treatment outcome. (3, 8)

In the market, there are many drug combinations of antidiabetic drugs, e.g., sitagliptin and metformin IR, (9-11) metformin and glipizide. (12,13) There are even triple drug combinations like metformin HCL, sitagliptin phosphate, and glimepiride. (14) An HPLC method has been reported for some of these products. In the present research, a novel fixed-dose combination tablet containing metformin HCl, sitagliptin phosphate, and glipizide was designed and developed as an immediate-release (IR) dosage form (DC IR tablet). In order to achieve the accuracy, precision, and reliability of drug content assessment, an HPLC technique is being developed and validated for the analysis of this novel combination in parallel with formulation development.

The formulation is proposed by replacing glimepiride with glipizide, a new combination like metformin HCL, sitagliptin phosphate, and glipizide, providing a safer and more balanced therapeutic option. The combination is strategically based on the marketed product, with glipizide substituted for glimepiride because of glipizide's shorter half-life, lesser potential for causing hypoglycemia, and lower association with weight gain. Older adults are more vulnerable to hypoglycemia, which can lead to falls, cognitive impairment, or cardiac events. In such cases, glipizide, which exerts good insulinotropic activity, can be used for a better safety profile for the long-term management of diabetes. This combination is more useful for people with comorbidities. Overall, emission of adverse effects through synergistic action increases efficacy, eventually providing better patient compliance and enhanced clinical outcome. (3,7)

Forced degradation

In the development of pharmaceutical products, forced degradation (FD), which is also known as stress testing. It is a necessary and important analytical technique that helps in determining the stability of medicinal ingredients and products. Stress conditions that are applied on samples are thermal degradation, acid-alkali hydrolysis, oxidative degradation, photolytic degradation, and effects of temperature. (15)

EXPERIMENTAL WORK

Materials

Chemicals and Reagents

All chemicals and ingredients that are used in this are analytical or HPLC grade for accuracy and reproducibility of all experiments. Methanol and HPLC-grade acetonitrile were purchased from Thermo Fisher Scientific India Pvt. Ltd. Orthophosphoric acid (AR grade) was received from Sisco Research Laboratories Pvt. Ltd. Potassium dihydrogen orthophosphate (AR grade) was received from SD Fine-Chem Ltd. The HPLC-grade water used in the entire chromatographic analysis was prepared with a Lab Q Ultra purification system.

Methods

HPLC Instrumentation and chromatographic conditions

Pharmaceutical compound analysis was performed on a Shimadzu LC 2030 HPLC system with a quaternary pump, autosampler, and column oven to provide a constant temperature throughout the run.

Chromatographic information was gathered and analyzed by LabSolutionssoftware. Separation of compounds was accomplished through an INERTSIL® ODS-3 V C18 column (250 × 4.6 mm, 5 µm) in reverse-phase operation.

The wavelength for detection was fixed at 230 nm to provide maximum analyte response. The mobile phase, which was pumped at a rate of 1 mL/min, included methanol, acetonitrile, and buffer (pH 3) in the ratio of 35:20:45% v/v/v. The total run duration was 15 minutes for each injection, and the column oven temperature was maintained at 30°C. Each sample received an injection of 10 µL. Prior to use, the buffer solution was also vacuum-filtered via a 0.25 µm Millipore membrane filter for purity and homogeneity.

Preparation of Dihydrogen Phosphate buffer pH 3:

After carefully measuring 1.36 g of potassium dihydrogen phosphate (AR grade), it was placed in a 1000 ml volumetric flask, and the volume was filled up with HPLC-grade water. To change the pH, O-phosphoric acid (OPA, AR Grade) was added. After 15 minutes of sonication, the solution was filtered through a 0.45 µm membrane filter before use.

Preparation of Mobile Phase:

35 ml of HPLC-grade methanol, 20 ml of HPLC-grade acetonitrile (ACN), and 45 ml of buffer are used as a mobile phase in a 35:20:45 ratio.

Preparation of diluent:

Based on the solubility of the API, the diluent was selected as methanol: ACN: buffer.

Preparation of Standard Solution:

Weigh 10 mg of the working standards for metformin HCL, sitagliptin phosphate, and glipizide accurately, and transfer the contents into different 10 mL volumetric flasks. To fully dissolve the medication, add 5 mL of methanol to each flask and sonicate for two to three minutes. After dissolving, add methanol to bring the volume up to 10 mL. 5 mL of the metformin HCL stock solution, 0.5 mL of the sitagliptin phosphate stock solution, and 0.05 mL of the glipizide stock solution should be carefully pipetted out into a 10 mL volumetric flask in order to prepare the standard combination. Dilute to volume with the appropriate diluent (methanol:ACN:buffer) to obtain final concentrations of 500 ppm metformin HCL, 50 ppm sitagliptin phosphate, and 5 ppm glipizide.

Preparation of Sample Solution:

10 tablets were coarsely crushed and weighed. A volumetric flask with a volume of 100 mL containing 500 mg of metformin HCl, 50 mg of sitagliptin phosphate, and 5 mg of glipizide was filled with the powder. After adding 50 milliliters of methanol, the sample solution was sonicated for fifteen minutes. After adding methanol to get the solution up to 100 mL, it was filtered using 0.45 µm Whatman filter paper. Later, the diluent (methanol:ACN:buffer) was added to 1 mL of the filtered solution, which had been precisely transferred to a 10 mL volumetric flask.

VALIDATION

System suitability

A system suitability test (SST) is a requirement to prove that a chromatographic system operates satisfactorily and produces reproducible results. Any concentration of the working range is selected, and six replicates are employed.

Specificity

Specificity is the capability to estimate analyte unambiguously in the presence of components that could reasonably be anticipated to be present. Method specificity was established by observing and comparing the obtained result for the sample solution with the standard result obtained from a pure drug and the blank chromatogram, standard drug, and sample.

Linearity

In every analytical technique, linearity is a very important parameter that reflects its capacity to give test results in direct proportion to the concentration of analyte in the sample (16). For the quantitation of analytes in the formulations, standard stock solutions have been diluted to achieve linearity of standard solutions (considering the quantitation limit) of metformin HCL, sitagliptin phosphate, and glipizide in the range of 200–800, 20–80, and 2–8 ppm, respectively. The standards were used in triplicate to create the calibration curve. The slope and intercept of the calibration curves and correlation coefficient (R^2) were used to calculate the linearity of the method.

Accuracy

The precision of an analytical method is the closeness of the accepted true value to the experimentally measured value of the test sample (16, 17). For evaluation of the precision of the developed method, recovery studies at three concentration levels, viz., 80%, 100%, and 120%, were performed on each of the active pharmaceutical ingredients, viz., Metformin HCL, Sitagliptin phosphate, and Glipizide. Specifically, 450 ppm, 500 ppm, and 550 ppm were used in the case of Metformin HCL; 45 ppm, 50 ppm, and 55 ppm for Sitagliptin phosphate; and 4.5 ppm, 5.0 ppm, and 5.5 ppm for Glipizide. Percentage recoveries for both drugs were calculated from values derived from spiked samples and were far within the acceptable range, suggesting that the method is reliable and accurate for quantitative estimation of the combined drug formulation.

Precision

The accuracy of an analysis method is called the measure of agreement of a series of measurements obtained from numerous samplings of a single homogeneous sample under specified conditions. (16, 17) System accuracy and method accuracy in this research were investigated by analyzing standard and sample solutions with the same concentration level six times under the same environment. For the intermediate precision, three varying levels of standard solution concentrations were estimated in triplicate and replicated thrice at regular intervals by multiple analysts on different days. The output indicated satisfactory %RSD values under all conditions, which establish the developed method as precise, reproducible, and dependable for routine analysis.

LOD and LOQ

The detection limit (LOD) is defined as the lowest amount of the analyte detected in the prepared sample. LOD can be calculated by using the following equation:

$$\text{LOD} = 3.3 \times \text{standard deviation of the response / slope of the calibration curve}$$

The quantitation limit (LOQ) is defined as the lowest amount of the analyte quantified with sufficient accuracy and precision. It can be calculated by using the following equation:

$$\text{LOQ} = 10 \times \text{standard deviation of the response / slope of the calibration curve}$$

For the following study, the LOD and LOQ were generated by the system itself.

Robustness

Robustness testing is a critical aspect of method development, as it examines how reliable and reproducible an analytical method is under minute planned changes in analysis conditions. Robustness of the HPLC method developed in the current study was determined by implementing minor variations in key parameters such as mobile phase volume, run time, wavelength used for detection, and column oven temperature. The results proved that the technique was not impacted by these intentional alterations, and consistent chromatographic results were achieved in all instances. This proves that the method established is robust and reliable for repeated use in the formulation analysis.

Forced Degradation

Thermal Degradation: A specific amount of the drugs was weighed out and placed into a china dish, which was covered with aluminium foil. A mixed standard solution of the three drugs was prepared and stored at higher temperature (60°C, 4 hours). After heating, the samples were conditioned at room temperature and then analyzed by HPLC.

Acid and Alkali Hydrolysis: The standard combined solution was subjected to acidic and basic hydrolysis by the addition of 0.1N HCl and 0.1N NaOH, respectively, and left at room temperature for 2 hours. Neutralization of the reaction was done with an appropriate volume of NaOH or HCl after hydrolysis. The samples were treated and analyzed with HPLC for assessing the extent of degradation.

Oxidative Degradation: Working solutions of active pharmaceutical ingredients (APIs) were prepared in a serial dilution using 3% (v/v) aqueous solution of hydrogen peroxide (H_2O_2), which acted as both oxidizing agent and solvent. The solution was then allowed to react for 2 hours prior to being analyzed for oxidative degradation through HPLC.

Photolytic Degradation: All three drugs stock solutions were placed in a UV chamber (EXPO HI-TECH) for 24 hours at room temperature. After the exposure period, the solutions were diluted, and the resulting solutions were analyzed with HPLC to determine the photolytic degradation.

Effect of Temperature: The referred drugs combined standard solution was kept under incubation at three different temperature conditions, i.e., 25°C, 40°C and 60°C, and each of the sample was in triplicate. After having an incubation period of two hours for each of the specified temperature, the sample was taken for HPLC analysis for timing component quantification. The results were compared to assess the consequences of the temperature difference.

FORMULATION DEVELOPMENT

Formulation trails

A direct compression immediate-release tablet of Metformin HCl, Sitagliptin, and Glipizide was formulated to deliver effective glycemic control in Type 2 Diabetes Mellitus. The formulation made use of Sodium Starch Glycolate (SSG) as a superdisintegrant to provide a quick disintegration of the tablet with a rapid onset of action. Lactose Anhydrous and Microcrystalline Cellulose (MCC) were employed as diluents to enhance blend uniformity and compressibility. Talc and Magnesium Stearate in concentrations of 1% each were used as glidant and lubricant, respectively, to improve powder flow and to stop sticking on compression. The tablet weight was kept at a total of 795mg, and the overall formulation composition is listed in table no. 1.

Tablet preparation procedure

Tablet formulation process included a number of key steps:-

Step 1 (Dispensing) - All the ingredients were weighed correctly.

Step 2 (Sifting) - Active pharmaceutical ingredient (API) was sieved through a #40 sieve and poured into a poly bag. Likewise, excipients like sodium starch glycolate, lactose anhydrous, and microcrystalline cellulose were sifted through a #40 sieve and blended together. Talc and magnesium stearate were sifted separately through a #60 sieve and collected.

Step 3 (Dry Mixing) – The sifted API and excipients were transferred to an octagonal blender and mixed for 10 minutes at 15 RPM.

Step 4 (Lubrication) - The blend was lubricated with talc and magnesium stearate in the same blender for 3 minutes at 15 RPM. After lubrication, physical parameters such as bulk density, tapped density, compressibility index, Hausner's ratio, loss on drying, and particle size distribution were evaluated.

Step 5 (Compression) - Finally, the lubricated blend was compressed into tablets using 12 mm round, standard convex punches.

Pre compression study

Pre-compression studies were conducted for the DC IR antidiabetic tablet, which consisted of metformin HCL, sitagliptin phosphate, and glipizide. The physical properties of the powder blend prior to tablet compression were studied; these studies included the examination of bulk density, tapped density, compressibility index, Hausner's ratio, loss on drying, and particle size distribution. These parameters are critical to ensure proper flowability, uniformity, and compressibility of the blend, which directly influence the quality and consistency of the final tablet. The results from the pre-compression evaluation help in optimizing the formulation and ensuring smooth tablet manufacturing during large-scale production.

Post compression study

Post-compression analyses of the DC IR antidiabetic tablet were carried out for testing the quality and uniformity of the final compressed tablets. The studies involved tablet weight variation, hardness, thickness, friability, disintegration time, content uniformity of drug, and in vitro dissolution profile. These tests are vital to ensure that the tablets meet pharmacopeial specifications and deliver the intended therapeutic action. These findings confirmed the stability, homogeneity, and appropriate drug release pattern of the formulation and validated its sustainability for further development and possible scaling.

In vitro drug release study

In vitro dissolution testing of oral solid dosage forms plays a significant part in product uniformity and formulation optimization, in the course of development. It measures the amount of drug dissolved in a medium at different times, typically 0 to 60 minutes, under controlled conditions. The test can be used to assess dosage form performance, interpret drug release profiles, and determine batch-to-batch similarity. It is also useful for bioavailability and bioequivalence testing. Dissolution was conducted on five batches over 60 minutes. Their dissolution profiles were compared. This is a basic piece of information for formulation development and quality control.

Assay

An assay is a test procedure applied to measure the quantity of an active pharmaceutical ingredient (API) in a formulation. Besides ascertaining the presence of the drug, it determines its precise concentration and, in certain instances, its biological or pharmacologic activity. Assay testing is necessary to verify that the formulation complies with stated requirements and contains the right amount of the active ingredient as labeled. The assay was performed on the last formulation to determine the drug content and to further validate the drug content consistency with the labeled quantity.

Stability study

Stability testing is performed to establish how the quality of a pharmaceutical product or an active substance alters with time under the influence of environmental conditions such as temperature, humidity, and light. Product-related conditions, such as the characteristics of the active substance, excipients, dosage form, manufacturing process, and packaging materials, influence stability as well. Stability of potentially degradable excipients that may produce reactive products is also taken into consideration. On the basis of results, product shelf life can be recommended. In the current investigation, the ultimate formulation was placed at 25°C/60% RH, 30°C/75% RH, and 40°C/75% RH for 2 months. Physical appearance, drug content, and release profile were analyzed after the first and second months to check stability under these conditions.

RESULTS

Optimization of chromatographic condition:

The chromatographic run was done on an Inertsil® ODS-3V C18 column of size 250 × 4.6 mm and a particle size of 5 µm under isocratic mode of elution. The mobile phase was methanol:acetonitrile:buffer in the proportion of 35:20:45 (v/v/v). The same mobile phase was employed as the diluent. The flow rate was 1.0 mL/min, and the injection volume was 10 µL. Column oven temperature was maintained at 30°C, and detection was performed with the help of a UV detector at a wavelength of 230 nm.

The entire run time for each analysis was 15 minutes. Retention times (RT) of the analytes were recorded as follows: Metformin HCL appeared at 2.3 minutes, sitagliptin phosphate at 3.3 minutes, and glipizide appeared at 13.7 minutes. The system was equilibrated with the diluent as blank and all the chromatographic conditions were maximized to deliver excellent resolution, symmetry of peaks, and reproducibility. Table no. 2

System suitability:

It was carried out according to ICH guidelines, and all those parameters that were to be tested were within the range of acceptance limits stated and listed in table no. 3. The tailing factor was below 2, the number of theoretical plates (NTP) was greater than 2000, and the resolution was greater than 2. Due to this information, it can be calculated that the developed method is accurate.

Specificity:

Specificity is the ability to assess an analyte unequivocally in the presence of components that may be expected to be present. Method specificity was determined by observing and comparing the result obtained for the sample solution with the standard result obtained for a pure drug and the chromatograms of the blank, standard drug, and sample shown in Figures no. (4), (5), and (6).

Linearity:

The linearity of the HPLC method developed was confirmed for Metformin HCL (200–800 ppm), Sitagliptin phosphate (20–80 ppm), and Glipizide (2–8 ppm) at seven different concentration levels with 25% to 175% target concentration. The method had excellent linearity with correlation coefficients (R^2) of 0.9994 for Metformin HCL, 0.9993 for Sitagliptin phosphate, and 0.9991 for Glipizide. The slopes were 5403.7, 3021.3, and 510,428, respectively, and the intercepts were 937,206, 44,624, and 729,558, showing good linear correlation between concentration and peak area for all three drugs. These results prove that the method is linear, precise, and reliable for quantitative determination over the concentration ranges examined. Linearity data is shown in table no. 4.

Accuracy:

The accuracy and reproducibility of the proposed method were tested in a recovery experiment. A formulated sample was taken, and the standard drug (API – Metformin HCL, Sitagliptin phosphate, and Glipizide) was added at 80%, 100%, and 120% levels. Each level was repeated three times. The content of metformin HCL, sitagliptin phosphate, and glipizide found by the proposed method is shown in Table no. 5. The mean recovery of Metformin HCL, Sitagliptin phosphate, and Glipizide was 99.88%, 99.88%,99.62% and 99.98%, respectively.

Precision:

Precision of an analytical procedure expresses the closeness of agreement between a series of measurements obtained from multiple samplings of the same sample under the prescribed conditions.

System precision was performed by injecting six replicate injections of standard solution of Metformin HCL (500 ppm), Sitagliptin phosphate (50 ppm), and Glipizide (5 ppm). The average, standard deviation (SD), and % RSD of area in six replicate injections were calculated and reported.

Method precision was performed by injecting 6 replicate injections of sample solutions of Metformin HCL (500 ppm), Sitagliptin phosphate (50 ppm), and Glipizide (5 ppm), and the % assay, average, standard deviation (SD), and %RSD were calculated and reported.

Intermediate precision was performed by two methods: different analysts and interday precision. The working concentration solution was analyzed for three consecutive days to perform interday precision and was also analyzed by three different analysts. Peak areas were obtained from the analysis, and the % RSD was found to be less than 2.

The results of system precision, method precision, and intermediate precision are summarized in Tables no. 6, 7, and 8.

Limits of Detection (LOD) and Limits of Quantification (LOQ):

LOD and LOQ of Metformin HCL, Sitagliptin phosphate, and Glipizide were calculated using the response standard deviation and calibration curve slope according to ICH guidelines. The Limit of Detection (LOD) values (Table no. 9) were 37.03 ppm for

Metformin HCL, 5.2 ppm for Sitagliptin phosphate, and 0.55 ppm for Glipizide. The corresponding Limit of Quantification (LOQ) values were (Table no. 9) 112.2 ppm, 15.77 ppm, and 1.67 ppm, respectively. These findings suggest that the developed HPLC method is adequately sensitive for the detection and quantification of all three drugs at low concentration levels.

Robustness:

Robustness of an analytical procedure is a measure of its capacity to remain unaffected by small but deliberate variations in method parameters and provides an indication of its reliability during normal usage. This was done by small deliberate changes in chromatographic conditions at 4 different levels, and the retention time of Metformin HCL, Sitagliptin phosphate, and Glipizide was noted. The factors selected were flow rate, wavelength, column temperature, and mobile phase. It was observed that there were no significant changes in the chromatogram, which demonstrates that the RP-HPLC method developed is robust. Results are described in Tables no. 10, 11, and 12.

Forced Degradation:

Forced degradation studies were performed to establish the stability-indicating nature of the HPLC method developed and to observe the degradation profile of Metformin HCL, Sitagliptin phosphate, and Glipizide under different stress conditions.

These materials were also stable under 25°C and 40°C mild heat stress with >98% recovery and <2% degradation. At 60°C, a considerable amount of degradation was observed: Metformin HCL (7.62%), Sitagliptin phosphate (10.93%), and Glipizide (10.67%), exhibiting moderate thermal sensitivity at higher temperatures. Three drugs under photolytic, oxidative, and dry heat stress conditions degraded very heavily, especially Sitagliptin phosphate and Glipizide. The maximum degradation was brought about by oxidative stress, and the recoveries dropped to ~80% while degradant formation was close to 19% for both APIs. This points towards vulnerability of the drugs towards peroxide-induced degradation.

Moderate degradation was noticed in acidic and basic hydrolysis for all drugs, Sitagliptin phosphate being the most degraded under both conditions (max. 18.52% degradation in acid, 16.81% in base). These findings indicate possible hydrolytic instability of Sitagliptin under both extremes of pH.

Overall, the degradation profile confirms the successful separation of the APIs from their degradants by the RP-HPLC method, proving it a potential stability-indicating method, as evident in table no. 13. It needs to be used for long-term storage, development of formulation, and regulatory submission.

Pre compression study:

The initial study of the individual drug powders, Metformin HCL, Sitagliptin phosphate, and Glipizide was conducted for determining the flow and compressibility properties of them. Metformin HCL, Sitagliptin phosphate, and Glipizide possessed bulk densities of 0.454, 0.542, and 0.357 g/mL and tapped densities of 0.667, 0.782, and 0.417 g/mL, respectively. The values of Carr's Index were 31.94% for Metformin HCL, 30.7% for Sitagliptin phosphate, and 14.4% for Glipizide, and the corresponding Hausner's ratios were 1.47, 1.44, and 1.16. The angle of repose was determined as 33.43° for Metformin HCL, 38.66° for Sitagliptin phosphate, and 41.2° for Glipizide. According to these values, Metformin HCL and Sitagliptin phosphate had poor flow characteristics, while Glipizide had very poor flowability, which needs flow-improving excipients methods when formulating tablets. Shown in table no. 14.

Post compression study:

Post-compression testing of all five tablet batches was conducted to determine key quality attributes, such as weight variation, hardness, thickness, friability, and disintegration time. The mean tablet weight across all batches was uniform, varying from 795.0 to 795.5 mg, signifying good content uniformity. Tablet hardness also reduced sequentially from 8.9 kg/cm² in Batch 1 to 4.5 kg/cm² in Batch 5, whereas tablet thickness was relatively consistent in all batches, varying between 4.2 and 4.3 mm. Friability measures were within satisfactory ranges (<1%) for Batches 1 to 4 but slightly increased to 1.1% in Batch 5, indicating minimal mechanical weakness at lower hardness. Disintegration time reduced consistently from 5.7 minutes in Batch 1 to 1.8 minutes in Batch 5, which corresponded to the impact of formulation variation, specifically superdisintegrant concentration. Among all, Batch 3 demonstrated a well-balanced profile with satisfactory hardness (6.4 kg/cm²), minimal friability (0.7%), and fast disintegration (3.6 min), justifying its choice as the optimized batch for future research. Shown in table no. 15.

In vitro drug release study:

The all five formulated batches of metformin HCl, sitagliptin phosphate, and glipizide monophasic immediate-release drug release profiles indicated 89% to 100% release in 60 minutes and 56% to 73% release in 30 minutes. Though all batches had less than 80% release in 30 minutes, Batch 3 had the most stable and uniform profile, with 73% release in 30 minutes and more than 97% in 60 minutes. While Batch 5 was released faster, it showed low hardness and high friability, which constrained its utility. but , Batch 1 had good hardness and decomposed slowly. Batches two and four were imbalanced. The best overall drug release, tablet hardness, friability, flowability, and excipient efficiency combination was shown by batch 3, the perfect formulation. Release of drug shown in figure no. (7).

Optimized batch:

Produced best performance under pre-compression, post-compression, and in vitro dissolution tests resulted in choosing the optimized formulation, otherwise known as Batch No. 3. metformin HCl, sitagliptin phosphate, and glipizide comprised the active pharmaceutical ingredients of the batch. Additionally, the formulation included talc and magnesium stearate as a lubricant and glidant, respectively, lactose anhydrous and microcrystalline cellulose as diluents, and sodium starch glycolate (SSG) as a superdisintegrant. The combination of all the 3 API and excipients provided the tablet with its desirable properties, such as consistent drug release, fast disintegration, and mechanical strength. Table No. 16 contains all the amounts of ingredients in the optimized batch. This formula was found to be most ideally suited for further testing on the basis of total performance.

Assay:

The assay of developed DC immediate-release tablets' was carried out, and the procedure outlined are follows the IP to determine the drug content of every formulation. The %assay of Metformin HCL was 99.99%, which falls within the 90–110% range given in the IP. The assay of sitagliptin phosphate and glipizide were 100.32% and 98.79%, respectively, both within the IP acceptable range of 98–102%. These ensure that the formulation prepared meets the content uniformity standard as per IP, confirming the reliability and correctness of the procedure.

Stability study:

The stability study of the optimized DC immediate-release tablet formulation (Batch No. 3) was checked under various storage conditions for a duration of two months according to ICH guidelines. The parameters studied such as appearance, tablet weight, in vitro dissolution, disintegration time, and drug content. As demonstrated in Table 17, the tablets of all five batches maintained their physical appearance and functional integrity under both normal (25°C/60% RH) and intermediate (30°C/75% RH) conditions of storage with no visible change in appearance, disintegration time, or drug release pattern. The 30-minute dissolution of optimized batch was consistent at around 73%, and drug content was over 99.8%, indicating excellent stability. Under accelerated conditions (40°C/75% RH), slight discoloration the change in color white to off-white, along with the loss in dissolution (52.90%) and a slight decrease in drug content (98.70%). The disintegration time prolonged slightly to 4.2 minutes, yet all values fell in the pharmacopeial range. All these findings ascertain that under normal and intermediate conditions, the formulation remains stable for two months and only minimally degraded at accelerated conditions. Long-term stability testing is suggested to validate the shelf life and stability of the formulation that has been optimized.

DISCUSSION

The main aim of this study was to formulate a safer, more efficient immediate-release (IR) tablet formulation of Metformin HCL, Sitagliptin phosphate, and Glipizide for the treatment of Type 2 Diabetes Mellitus (T2DM), along with the development and validation of a reliable RP-HPLC analytical technique for simultaneous estimation of these three drugs in the formulation. The reason for substituting Glimepiride for Glipizide was on the basis of robust clinical rationale—Glipizide has fewer risks of hypoglycemia, less weight gain, and a better safety profile in older or comorbid patients because it has a shorter half-life and lower cardiovascular risk. It was therefore a better sulfonylurea to have on board in a new fixed-dose combination (FDC).

The chromatographic conditions optimized during this research (methanol: acetonitrile: buffer at 35:20:45, isocratic mode, 1.0 mL/min, UV detection at 230 nm) ensured distinct separation of Metformin HCL, Sitagliptin phosphate, and Glipizide with retention times of 2.3, 3.3, and 13.7 minutes, respectively. This indicates high resolution and peak symmetry, reflecting the efficacy and reproducibility of the method. System suitability factors like tailing factor, theoretical plates, and resolution were all within ICH acceptance limits, further validating method robustness.

Method validation was adequately carried out in compliance with ICH Q2 (R1) regulations. The method showed specificity with no interference from excipients or degradation products and excellent linearity ($R^2 > 0.999$) across a broad concentration range. Accuracy and precision studies indicated % recoveries in the range of 99.6–100% and %RSD being far less than 2%, establishing the reliability of the method for routine application. Further validation of the method's sensitivity was established through the low LOD and LOQ values, which rendered the method applicable even for trace-level determination.

Forced degradation studies confirmed the ability of the method to separate and identify degradation products from several stress conditions, which include acid, base, oxidation, thermal, and photolytic degradation. This makes the method stability-indicating, which is crucial for quality control and regulatory compliance.

From the formulation point of view, pre-compression studies revealed unsatisfactory flow properties of active pharmaceutical ingredients (APIs), which were suitably addressed with the incorporation of appropriate excipients. Batch 3 was remarked among the five trial formulations as optimized batch that showed ideal parameter values for hardness, friability, disintegration time, and uniformity. Importantly, Batch 3 discharged over 73% of the drug within 30 minutes, hence meeting IP requirements for immediate-release tablets.

The optimized batch performed extremely well in short-term stability studies under regular and intermediate ICH conditions (25°C/60% RH and 30°C/75% RH) without any apparent physical or chemical degradation. Even at accelerated conditions (40°C/75% RH), though minimal changes were observed, the formulation remained within pharmacopeial limits, demonstrating satisfactory stability until the tested period. Additional long-term studies are necessary to establish its shelf life.

The novel fixed-dose combination of metformin HCL, sitagliptin phosphate, and glipizide therefore holds great therapeutic potential as an alternative to T2DM management, particularly in the elderly or high-risk patient groups. The triad action of the three drugs provides holistic glycemic control through interference with distinct mechanisms (insulin sensitivity, insulin secretion, and incretin action), reducing side effects usually seen with sulfonylurea-based combinations, such as those that include glimepiride.

CONCLUSION

The developed RP-HPLC technique based on methanol, ACN, and buffer as the mobile phase offers an accurate and robust strategy for estimating metformin HCL, sitagliptin phosphate, and glipizide simultaneously. As a truly capable method owing to its notable precision, robustness, and high accuracy, the technique holds sound potential in pharmaceutical quality control, routine operations, and laboratory-level analytical techniques in the pharmacy line of operations. It can be efficiently applied for simultaneous determination of these compounds in drug products and bulk material, with an assurance that quality control and regulatory compliance are always maintained.

REFERENCES

1. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 14219, Metformin Hydrochloride. Retrieved March 13, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Metformin-Hydrochloride. 26 - (1)
2. Srinivasa Rao, N., Venkataramana, D., & Naidu Srinivasa Rao, A. (2015). STABILITY-INDICATING RP-HPLC METHOD AND ITS VALIDATION FOR ANALYSIS OF METFORMIN HCL HYDROCHLORIDE & SITAGLIPTIN PHOSPHATE PHOSPHATE IN BULK AND PHARMACEUTICAL DOSAGE FORM. *Naidu et al. World Journal of Pharmaceutical Research World Journal of Pharmaceutical Research SJIF Impact Factor 5*, *4*(2), 649–662. www.wjpr.net (2)
3. Hong, J., Zhang, Y., Lai, S., Lv, A., Su, Q., Dong, Y., Zhou, Z., Tang, W., Zhao, J., Cui, L., Zou, D., Wang, D., Li, H., Liu, C., Wu, G., Shen, J., Zhu, D., Wang, W., Shen, W., & Ning, G. (2013). Effects of Metformin HCL Versus Glipizide on Cardiovascular Outcomes in Patients With Type 2 Diabetes and Coronary Artery Disease. *Diabetes Care*, *36*(5), 1304–1311. https://doi.org/10.2337/DC12-0719 (3)
4. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 6451150, Sitagliptin Phosphate. Retrieved March 13, 2025 27 –(4)
from https://pubchem.ncbi.nlm.nih.gov/compound/Sitagliptin-Phosphate.
5. Sushma, G., Sri Harsha, D., & Mukthinuthalapati, M. A. (2020). New first derivative spectrophotometric methods for the determination of sitagliptin-an antidiabetic agent. *Research Journal of Pharmacy and Technology*, *13*(6), 2838–2842. https://doi.org/10.5958/0974-360X.2020.00505.3 30 - (5)
6. *Gunuputi Sushma, Sri Harsha D, Mathrusri Annapurna Mukthinuthalapati. New first derivative spectrophotometric methods for the determination of Sitagliptin phosphate - An antidiabetic agent. Research J. Pharm. and Tech 2020; 13(6): 2838-2842. doi: 10.5958/0974-360X.2020.00505.3 (6)*
7. National Center for Biotechnology Information (2025). PubChem Compound Summary for CID 3478, Glipizide. Retrieved March 13, 2025 from https://pubchem.ncbi.nlm.nih.gov/compound/Glipizide 28 - (7)

8. Douros, A., Yin, H., Yu, O. H. Y., Filion, K. B., Azoulay, L., & Suissa, S. (2017). Pharmacologic Differences of Sulfonylureas and the Risk of Adverse Cardiovascular and Hypoglycemic Events. Diabetes Care, 40(11), 1506–1513. https://doi.org/10.2337/DC17-0595
9. Krishnan B, Mishra K. Quality by Design based Development and Validation of RP-HPLC Method for Simultaneous Estimation of Sitagliptin and Metformin in Bulk and Pharmaceutical Dosage Forms. International Journal of Pharmaceutical Investigation. 2020 Oct 1;10(4).
10. Raza A, Murtaza SH, Hanif S, Iqbal J, Ali I, Aftab T, Shakir R, Bedar R, Syed MA. Validation of a rapid and economical RP-HPLC method for simultaneous determination of metformin hydrochloride and sitagliptin phosphate monohydrate: Greenness evaluation using AGREE score. Pakistan Journal of Pharmaceutical Sciences. 2022 Jan 1;35(1).
11. Ali M, Shah MR, Zairov R, Zafar S, Ali SI, Ansar F, Uddin KM, Akylbekov N. An efficient RP-HPLC-based approach for simultaneous determination of sitagliptin and metformin HCl in pharmaceutical drug formulation. Pakistan Journal of Pharmaceutical Sciences. 2024 May 1;37(3).
12. Bapusaheb BS, Jadhav Prerana B. Development and validation of RP-HPLC method for simultaneous estimation of metformin hydrochloride and glipizide in bulk and pharmaceutical dosage form. Drug Deliv.(nd). 2011.
13. Mandal S, Patel B, Bose A, Swamy G, Pandit SN, Goli D. Stability indicating assay method by HPLC for simultaneous estimation of Metformin and glipizide in bulk and pharmaceutical dosage form. World Journal of Pharmacy Pharmaceutical Sciences. 2015 Apr 13;4(6):1410-31.
14. Yadav, M., Chauhan, R., … R. S.-C., & 2025, undefined. (n.d.). Development And Validation Of RP-HPLC Method For Simultaneous Quantification Of Three Anti-Diabetic Agents In Pharmaceutical Formulation. *Cuestionesdefisioterapia.Com*, *54*(1), 715–720. Retrieved June 11, 2025, from https://cuestionesdefisioterapia.com/index.php/es/article/download/2231/1633
15. Blessy, M., Patel, R. D., Prajapati, P. N., & Agrawal, Y. K. (2014). Development of forced degradation and stability indicating studies of drugs—A review. *Journal of Pharmaceutical Analysis*, *4*(3), 159–165. https://doi.org/10.1016/J.JPHA.2013.09.003
16. "ICH (1996) International Conference of harmonization, validation of analytical procedures: text and methodology, guideline Q2(R1), Geneva, incorp. ," 2005.
17. K. Ferenczi-Fodor, B. Renger, and Z. Végh, "The frustrated reviewer — Recurrent failures in manuscripts describing validation of quantitative TLC/HPTLC procedures for analysis of pharmaceuticals," *Journal of Planar Chromatography – Modern TLC*, vol. 23, no. 3, pp. 173–179, Jun. 2010, doi: 10.1556/JPC.23.2010.3.1.

FIGURES

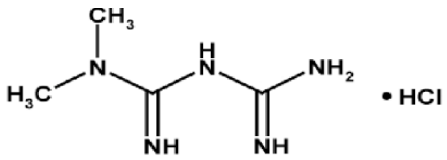

Fig. no. 1 Chemical structure of Metformin HCL

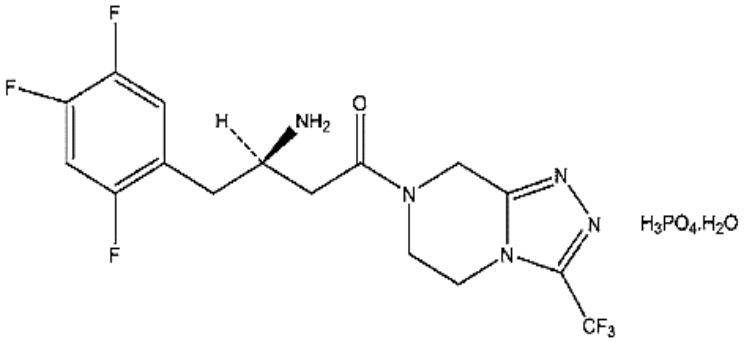

Fig. no. 2 Chemical structure of Sitagliptin phosphate

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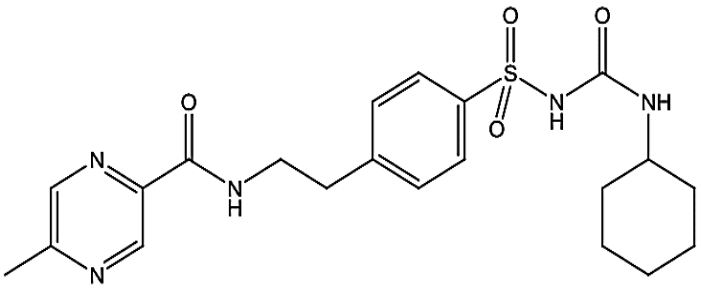

Fig. no. 3 Chemical structure of Glipizide

CHROMATOGRAM

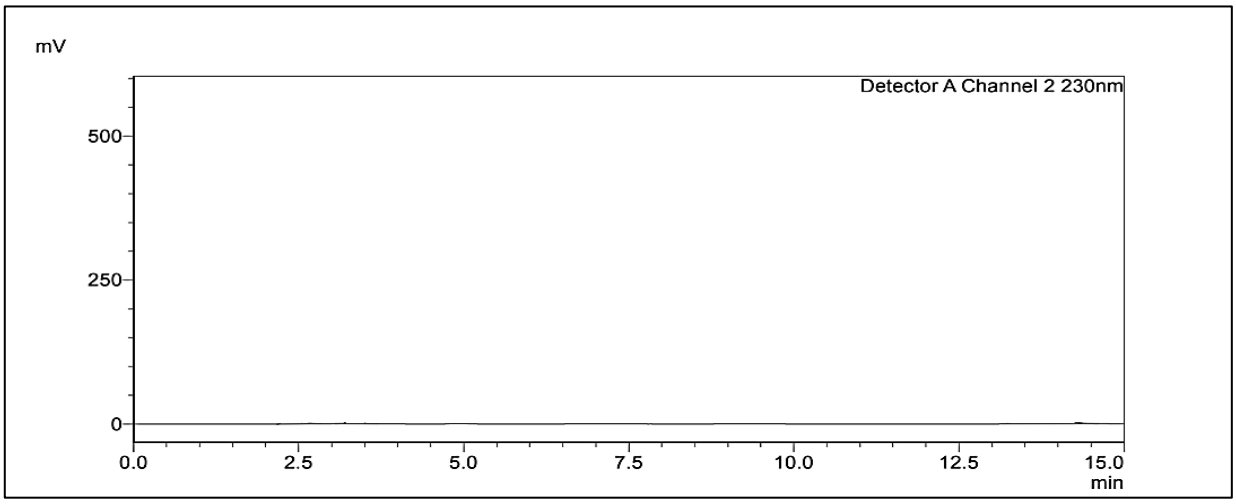

Figure no. (4) Chromatogram of Blank solution

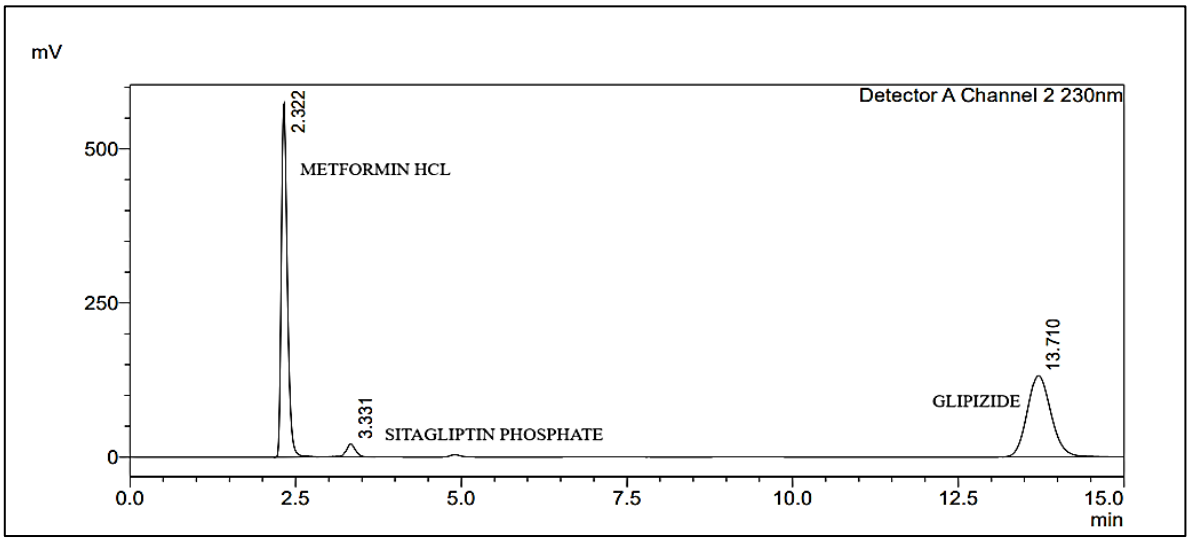

Figure no. (5) Chromatogram of Standard solution of Metformin HCL, Sitagliptin phosphate and Glipizide

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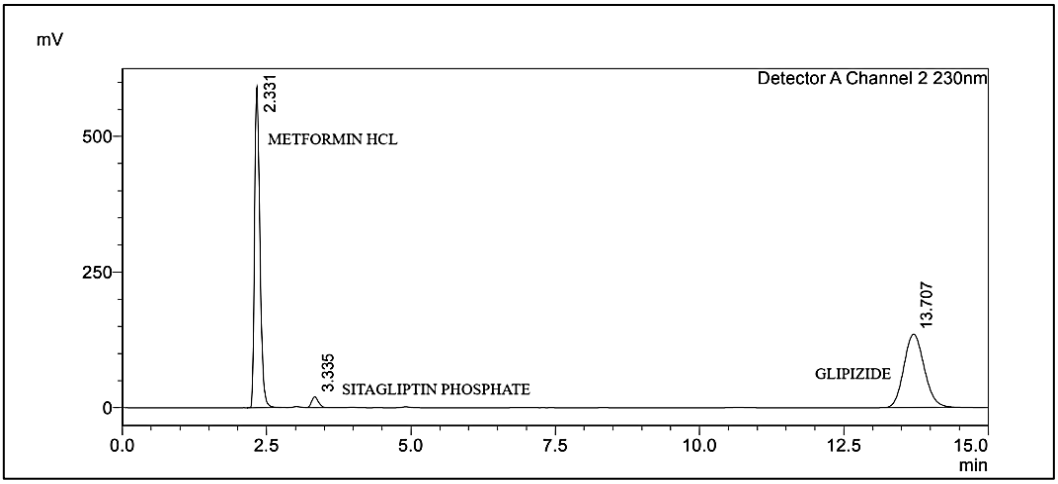

Figure no. (6) Chromatogram of Sample solution of Metformin HCL, Sitagliptin Graphs

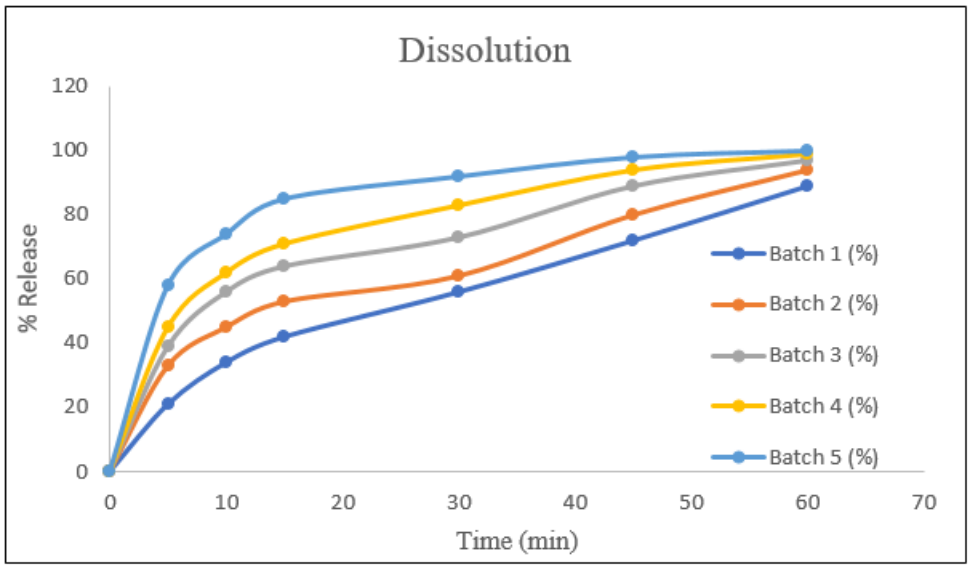

Figure no. (7) Dissolution Graph

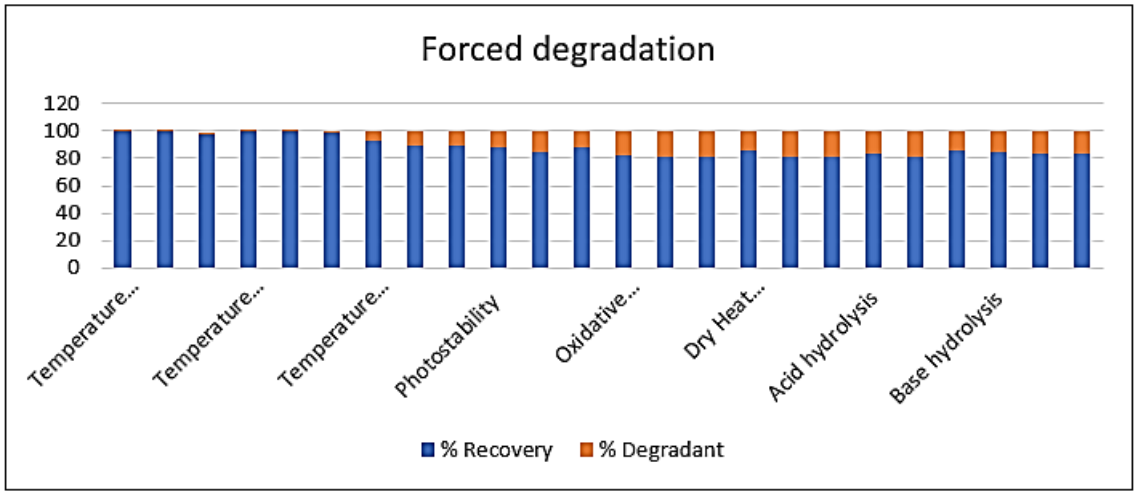

Figure no. (8) Dissolution Graph

TABLES

Table no. 1 Formulation trails

Ingredients	Batch 1 (mg)	Batch 2 (mg)	Batch 3 (mg)	Batch 4 (mg)	Batch 5 (mg)
Metformin HCl	500	500	500	500	500
Sitagliptin	50	50	50	50	50
Glipizide	5	5	5	5	5
Sodium Starch Glycolate (SSG)	90	100	110	120	130
Lactose Anhydrous	70	70	70	70	70
Microcrystalline cellulose (MCC)	80	70	60	50	40
Talc (1%)	7.95	7.95	7.95	7.95	7.95
Magnesium Stearate (1%)	7.95	7.95	7.95	7.95	7.95
Total Tablet Weight	795	795	795	795	795

Table no. 2 Optimized method

Parameter	Optimized condition
HPLC column	Inertsil® ODS- 3 V C18 (250 x 4.6 mm, 5 µm)
Flow rate	1mL/min
Injection volume	10 µL
Mobile Phase	Methanol : ACN: Buffer (35:20:45,v/v/v)
Diluent	Methanol : ACN: Buffer (MP used as diluent)
Column Oven Temperature	30°C
Detector	UV detector
Wavelength	230 nm
Run time	15 min
Pump mode	Isocratic
Blank	Diluent
Retention Time (RT)	Metformin HCL - 2.3 min
	Sitagliptin phosphate - 3.3 min
	Glipizide - 13.7 min

Table no. 3 System suitability data

Sr.no.	Parameter	Acceptance criteria	Metformin HCL	Sitagliptin phosphate	Glipizide
1	Retention Time (min)	-	2.3	3.3	13.7
2	Tailing Factor (TF)	Less than 2	1.336	1.219	1.125
3	No. of Theoretical Plate (NTP)	More than 2000	2691	3470	7193
4	Resolution	More than 2	-	4.945	23.764

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Table no. 4 Linearity value of Metformin HCL, Sitagliptin phosphate and Glipizide

Sr. no.	Level	Concentration of Metformin HCL (ppm)	Peak area of etformin HCL	Concentration of Sitagliptin phosphate (ppm)	Peak area of Sitagliptin phosphate	Concentration of Glipizide (ppm)	Peak area of Glipizide
1	25%	200	2055954	20	103484	2	1787158
2	50%	300	2517643	30	134643	3	2221326
3	75%	400	3092339	40	168149	4	2783013
4	100%	500	3619874	50	197129	5	3287962
5	125%	600	4194237	60	224129	6	3762433
6	150%	700	4748663	70	257110	7	4273295
7	175%	800	5244789	80	285164	8	4856700
Slope		5403.7		3021.3		510428	
Intercept		937206		44624		729558	
R^2		0.9994		0.9993		0.9991	

Table no. 5 Accuracy of Metformin HCL, Sitagliptin phosphate, Glipizide

Sr. no.	Name of the Drugs (n=3)	Level	Sample added (ppm)	Standard added (ppm)	Actual amount (ppm)	Amount Recovered (ppm)	% Recovery	Mean of % Recovery
1	Metformin HCL	80%	250	200	450	448.33	99.62889	99.87618
		100%	250	250	500	499.98	99.996	
		120%	250	300	550	550.02	100.0036	
2	Sitagliptin phosphate	80%	25	20	45	44.47	98.82222	99.6171
		100%	25	25	50	49.96	99.92	
		120%	25	30	55	55.06	100.1091	
3	Glipizide	80%	2.5	2	4.5	4.49	99.77778	99.98047
		100%	2.5	2.5	5	4.99	99.8	
		120%	2.5	3	5.5	5.52	100.3636	

Table no. 6 System precision

SYSTEM PRECISION AREA OF STANDARD			
Injection	**Metformin HCL**	**Sitagliptin phosphate**	**Glipizide**
1	3609127	198088	3297607
2	3613790	197222	3245426
3	3610831	197342	3265790
4	3612702	196368	3249957
5	3609209	197914	3270310
6	3609874	195452	3271199
Mean	3610922	197064.3	3266715
SD	1763.37	908.87	16942.32
%RSD	0.05	0.46	0.52

Table no. 7 Method precision

METHOD PRECISION AREA OF SAMPLE			
Injection	**Metformin HCL (%)**	**Sitagliptin phosphate (%)**	**Glipizide (%)**
1	99.56	100.1	98.79
2	100.3	99.95	98.72
3	100.2	99.72	98.89
4	99.63	100.2	98.69
5	99.89	99.84	99.32
6	100.2	99.69	98.89
Mean	99.96	99.92	98.88
SD	0.29	0.19	0.21
%RSD	0.29	0.19	0.21

Table no. 8 Intermediate precision

INTERMEDIATE PRECISION							
Different analyst	**Metformin HCL**	**Sitagliptin phosphate**	**Glipizide**	**Interday precision**	**Metformin HCL**	**Sitagliptin phosphate**	**Glipizide**
Analyst 1	3612402	195368	3249787	**Day 1**	3612402	194868	3249487
Analyst 2	3609509	199954	3270310	**Day 2**	3609509	198814	3271310
Analyst 3	3608474	197652	3281499	**Day3**	3608774	194472	3281499
Mean	3610128	197658	3267199	**Mean**	3610228	196051.3	3267432
SD	1662.32	1872.23	13131.97	**SD**	1566.03	1960.18	13353.43
%RSD	0.05	0.95	0.40	**%RSD**	0.04	0.99	0.41

Table no. 9 The value of LOD and LOQ of all the Drugs

Sr.no	Drug name	LOD (ppm)	LOQ (ppm)
1	Metformin HCL	37.03	112.2
2	Sitagliptin phosphate	5.2	15.77
3	Glipizide	0.55	1.67

Table no. 10 Result of Robustness for Metformin HCL

ROBUSTNESS FOR METFORMIN HCL							
Sr. no.	**Parameter (n=3)**	**Change in parameter**	**% estimation**	**Mean**	**SD**	**%RSD**	**Limit**
1	Wavelength (nm)	228	99.52	99.86	0.278	0.28	NMT 2%
		230	99.85				
		232	100.2				
2	Flow Rate (mL/min)	0.8	99.58	99.85	0.213	0.21	
		1	99.87				
		1.2	100.1				
3	Temperature (°C)	28	100.2	100.02	0.198	0.19	
		30	99.75				
		32	100.1				
4	Mobile phase (v/v/v)	34:20:45	99.93	99.99	0.177	0.18	
		34:21:45	100.2				
		35:19:46	99.75				
		35:20:45	99.86				
		35:21:44	99.95				
		36:19:45	99.98				
		36:20:44	100.3				

Table no. 11 Result of Robustness for Sitagliptin phosphate

ROBUSTNESS FOR SITAGLIPTIN PHOSPHATE							
Sr. no.	**Parameter (n=3)**	**Change in parameter**	**% Estimation**	**Mean**	**SD**	**%RSD**	**Limit**
1	Wavelength (nm)	228	99.75	99.96	0.186	0.19	NMT 2%
		230	99.92				
		232	100.2				
2	Flow Rate (mL/min)	0.8	99.53	99.62	0.156	0.156	
		1	99.49				
		1.2	99.84				
3	Temperature (°C)	28	99.89	100.09	0.167	0.17	
		30	100.3				
		32	100.1				
4	Mobile phase (v/v/v)	34:20:45	99.59	99.87	0.161	0.161	
		34:21:45	99.77				
		35:19:46	100.1				
		35:20:45	99.77				
		35:21:44	100				
		36:19:45	99.89				
		36:20:44	99.98				

Table no. 12 Result of Robustness for Glipizide

ROBUSTNESS FOR GLIPIZIDE							
Sr. no.	**Parameter (n=3)**	**Change in parameter**	**% Estimation**	**Mean**	**SD**	**%RSD**	**Limit**
1	Wavelength (nm)	228	98.59	98.72	0.217	0.22	NMT 2%
		230	98.55				
		232	99.03				
2	Flow Rate (mL/min)	0.8	99.08	99.1	0.213	0.21	
		1	98.85				
		1.2	99.37				
3	Temperature (°C)	28	98.58	98.82	0.175	0.18	
		30	98.89				
		32	98.99				
4	Mobile phase (v/v/v)	34:20:45	98.43	98.78	0.216	0.22	
		34:21:45	99.01				
		35:19:46	98.76				
		35:20:45	98.59				
		35:21:44	98.99				
		36:19:45	99.02				
		36:20:44	98.67				

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Table no. 13 Result of Robustness for Glipizide

Sr.no.	Stress condition	Drug name	% Recovery	% Degradant
1	Temperature 25°C	Metformin HCL	99.85	0.15
		Sitagliptin phosphate	99.5	0.5
		Glipizide	98.08	0.92
2	Temperature 40°C	Metformin HCL	99.96	0.04
		Sitagliptin phosphate	99.9	0.1
		Glipizide	98.26	1.74
3	Temperature 60°C	Metformin HCL	92.38	7.62
		Sitagliptin phosphate	89.07	10.93
		Glipizide	89.33	10.67
4	Photostability	Metformin HCL	87.7	12.3
		Sitagliptin phosphate	84.32	15.68
		Glipizide	88.5	11.5
5	Oxidative degradation	Metformin HCL	82.13	17.87
		Sitagliptin phosphate	80.93	19.07
		Glipizide	80.75	19.25
6	Dry heat degradation	Metformin HCL	85.67	14.33
		Sitagliptin phosphate	80.76	19.24
		Glipizide	80.93	19.07
7	Acid hydrolysis	Metformin HCL	83.87	16.13
		Sitagliptin phosphate	81.48	18.52
		Glipizide	85.92	14.08
8	Base hydrolysis	Metformin HCL	84.09	15.91
		Sitagliptin phosphate	83.19	16.81
		Glipizide	83.73	16.27

Table no. 14 The value of drug before compression

Parameter	Metformin HCL	Sitagliptin	Glipizide
Bulk Density (g/mL)	0.454	0.542	0.357
Tapped Density (g/mL)	0.667	0.782	0.417
Carr's Index (%)	31.94	30.7	14.4
Hausner's Ratio	1.47	1.44	1.16
Angle of Repose (°)	33.43	38.66	41.2
Flowability	Poor	poor	Very Poor

Table no. 15 The value of drug after compression

Parameter	Batch 1	Batch 2	Batch 3	Batch 4	Batch 5
Weight Variation (mg)	795.3	795.5	795.0	795.4	795.3
Hardness (kg/cm²)	8.9	7.5	6.4	5.3	4.5
Thickness (mm)	4.3	4.3	4.2	4.2	4.3
Friability (%)	0.55	0.6	0.7	0.9	1.1
Disintegration Time (min)	5.7	4.9	3.6	2.4	1.8

Table no. 16 Optimized Batch formula table

Sr. no.	Ingredients Optimized batch (mg)	Optimized batch (mg)
1	Metformin HCL	500
2	Sitagliptin	50
3	Glipizide	5
4	Sodium Starch Glycolate (SSG)	110
5	Lactose Anhydrous	70
6	Microcrystalline Cellulose	60
7	Talc (1%)	7.95
8	Magnesium Stearate (1%)	7.95
9	Total Tablet Weight	795

Table no. 17 Stability study of Optimized batch

Parameter	Initial	2 Months (25°C/60% RH)	2 Months (30°C/75% RH)	2 Months (40°C/75% RH)
Appearance	White, Convex round tablet	No change	No change	Slight discoloration (White to off white)
Weight (mg)	795 mg	795 mg	795 mg	795 mg
In Vitro Dissolution (%) (at 30 min)	73%	73%	72.6%	52.90%
Disintegration Time (min)	3.6 min	3.6 min	3.6 min	4.2 min
Drug Content (%) (UV at 230 nm)	99.89%	99.87%	99.84%	98.70%

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