# Validation of Stability Indicating RP-HPLC method for Simultaneous Estimation of Sitagliptin and Metformin HCl in Pharmaceutical Oral Solid Dosage Form

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***Abstract*- A Simple, Accurate and Precise Reverse Phase High Performance Liquid Chromatography (RP-HPLC) method for the simultaneous estimation of Sitagliptin (SITA) and Metformin HCl (MET) in marketed formulation was developed. The determination was carried out on Chromasol ONYX CN (4.6mm×250mm); 10µm column using a mobile phase Buffer: Acetonitrile (90:10v/v) by isocratic mode. The flow rate was1.0 ml / min with detection at 205nm and 232nm for Sitagliptin and Metformin Hcl.The retention time for Metformin HCl was 2.8 min and for Sitagliptin was 8.6min. Sitagliptin and Metformin HCl showed a linear response in the concentration range Sitagliptin as 5-7.5 µg/ml and Metformin HCl as 80 – 120 µg/ml for Respectively. The correlation co-efficient (' r ' value) for Sitagliptin and Metformin HCl was 1.000 and 0.9999 respectively. The percentage recoveries obtained for Sitagliptin and Metformin HCl ranges 99.7% and 101.1% respectively. The developed method was validated as per ICH Q2 R1 guidelines. For Specificity and linearity, Method Precision (Repeatability), Intermediate Precision (Ruggedness), Accuracy and Robustness the validation results were found well within the limits (%RSD of areas were <2 for assay and recoveries in the range of 98%-102% for assay, $r^2$>0.999) indicating that the developed method is simple, rapid, accurate, precise, specific, robust and economical and less time consuming and was successfully applied for Simultaneous estimation of Sitagliptin and Metformin HCl.**

***Keywords:*** **RP-HPLC method, Sitagliptin, Metformin HCl, ICH.**

## I. INTRODUCTION

Sitagliptin phosphate monohydrate ($C_{16}H_{20}F_6N_5O_6P$) chemically, (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 hydrate .It is a White to off-white crystalline, non-hygroscopic powder. It is soluble in water and N, N-dimethyl formamide; slightly soluble in methanol; Very slightly soluble in ethanol, acetone, and acetonitrile; and insoluble in isopropanol is oral hypoglycemic drug of the dipeptidyl peptidase-4 (DPP-4) inhibitor class. DPP-4 inhibitors represent a new therapeutic approach to the treatment of type 2 diabetes that functions to stimulate glucose-dependent insulin release and reduce glucagon's levels. This is done through inhibition of the inactivation of in cretins, particularly glucagon-like peptide- 1 (GLP-1) and gastric inhibitory polypeptide (GIP), thereby improving glycemic control. Metformin hydrochloride ($C_4H_{11}N_5$.HCl) is 1; 1-dimethylbiguanidine monohydrochloride. It is a White to off-white crystalline, non-hygroscopic powder. Freely soluble in water, slightly soluble in Alcohol, practically insoluble in Acetone and in Methylene chloride. It's an anti-diabetic drug from the Biguanide class of oral hypoglycaemic agents, given orally in the treatment of non – insulin-dependent diabetes mellitus. Major action of metformin HCl in increasing glucose transport across the cell membrane in skeletal muscle.

Recently, the combination of Sitagliptin and Metformin HCl has been recommended for use in the treatment of diabetes mellitus to improve glycemic control. Already few methods were reported for the determination of sitagliptin in pharmaceutical formulations or biological samples by spectrophotometry and HPLC. Analytical methods for determination of metformin include normal phase chromatography (silica and cyano), cation ex-change chromatography, ion pair chromatography and reversed phase chromatography with UV or mass spectrometric detection. The present work presents development and validation of a new and simple RP-HPLC method for simultaneous determination of metformin hydrochloride and sitagliptin phosphate in a formulation.

**Fig 1: Sitagliptin Phosphate Monohydrate**

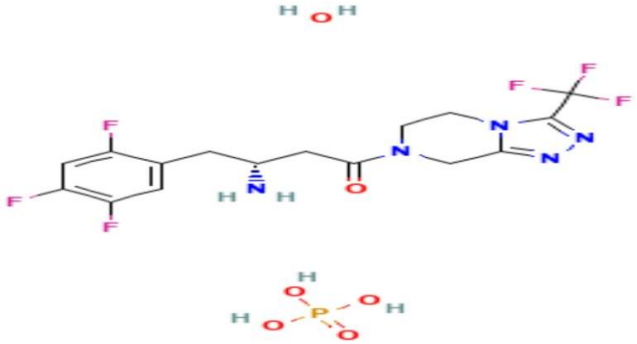
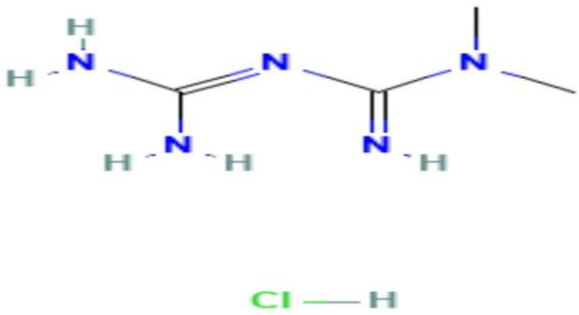


**Fig 2: Metformin HCl**



## II. EXPERIMENTAL

**Materials and Reagents**

Sitagliptin Phosphate Monohydrate and Metformin Hydrochloride was obtained as gift sample for research purpose. HPLC grade Acetonitrile (ACN) were purchased from Merck Specialities (Mumbai, India), Analytical grade or Equivalent Orthophosphoric Acid (OPA) were purchased from Avantor™ (RANKEM™ , Maharashtra), Milli – Q water Or Equivalent

**Instrumentation**

The development and validation of the method were performed on a HPLC System Alliance®Waters model 2695 with Empower 3 software version 2.0 was applied for data collection and processing. Detector waters 2489 UV/Vis detector. PH meter, Labindia Pico+. Analytical balance (semi micron balance) AS82/220.X2 RADWAG.

## III. METHODOLOGY

**Preparation of Mobile Phase**

**Buffer Solution –** 1000ml of Milli-Q water and adjust the PH 3.0 with orthophosphoric acid

Degassed mixture of Buffer Solution and Acetonitrile in the ratio of 90:10 v/v. Filter through 0.45µ Membrane filter.

**Preparation of Diluent**

**0.1% Orthophosphoric Acid –** 1ml Orthophosphoric Acid in 1000ml of Milli-Q water and mix.

**Diluent 1-** 0.1% Orthophosphoric acid and Acetonitrile in the ratio of 95:5 v/v.

**Diluent 2** – Water

**Selection of analytical wavelength**

The working standards of MET (100µg/mL) and SITA (6.3µg/mL) were prepared in diluent and inject in HPLC equipped with PDA-detector. The spectra of SITA and MET were overlapped 205nm and 232nm were selected as analytical wavelength for quantitative determination of SITA and MET.

**Preparation of Sitagliptin Phosphate Standard Solution (Conc about 5ppm)**

Weigh and transfer 64mg of Sitagliptin Phosphate working and transfer into 50ml clean, dry volumetric Flask, , Add about 20mlof diluent 1 ( 0.1% OPA:ACN (95:5v/v) )and sonicate to dissolve. Make up the volume with diluent 1 up to the mark and mix well. Cool the solution to Room temperature and further dilute the above solution 5ml into 50ml volumetric flask and makeup the Volume with diluent 2 (Water) and mixed well.

**Preparation of Standard Solution**

Weigh and transfer 50mg of Metformin Hydrochloride working and transfer into 50ml clean, dry Volumetric flask, Add about 20mlof diluent 1 ( OPA: ACN (95:5v/v)) and sonicate to dissolve. Make up the volume with diluent 1 up to the mark and mix well. Cool the Solution to room temperature and further dilute the above solution 10ml and add 5ml of Sitagliptin Phosphate stock standard solutions into 100ml volumetric flask and makeup the volume with diluent 2 and Mixed well.

**Preparation of Sample Solution**

Weight and transfer 10 tablets into 1000ml clean, dry volumetric flask, as dropping method and add 10ml of diluent 2 (Water) to disintegrate the tablet and sonicate for 5 min further add 750ml of diluent 1(OPA : ACN (95:5v/v) ) and sonicate for 15 mins ( Intermittent shaking) . Cool the solution to room Temperature and Make up the volume with diluent 1 up to the mark and mix well. Further dilute the above clear solution into 50ml volumetric flask, dilute the solution with diluent 2 and makeup the volume and mixed well. Further dilute the above clear solution 5ml into 50ml volumetric flask, dilute the solution with diluent 2 and makeup the volume and mixed well. Filter the sample solution through 0.45µ PVDF Filter.

**Selection of Mobile Phase for Method Optimization and Experimental Condition**

Several trials have been taken for the proper optimization of RP HPLC method by changing different mobile phase With different ratio. And finally the mobile phase for optimized condition was selected and given follows. And the Optimized parameters was for SITA and MET was given (Table 1).

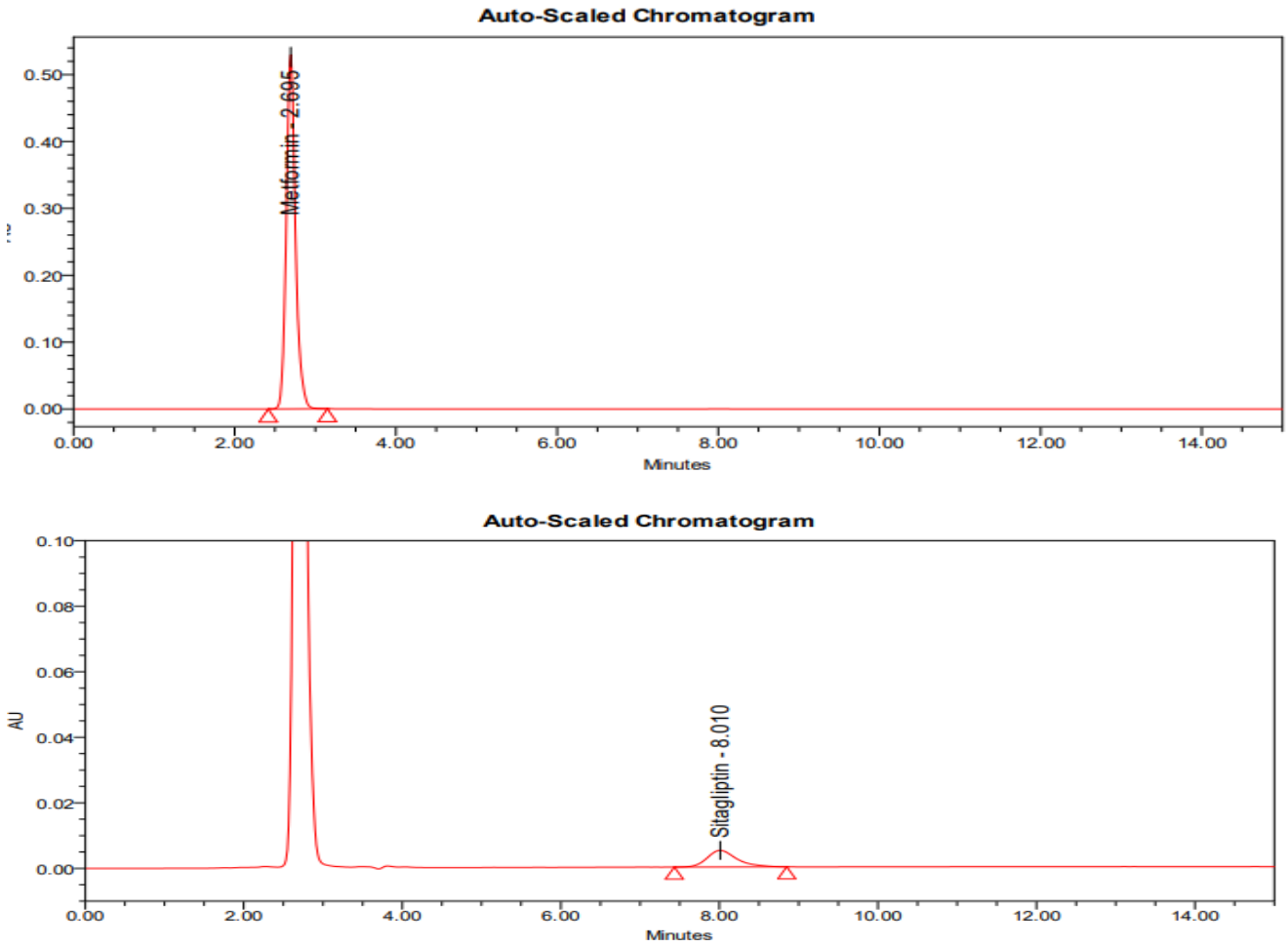



**Fig 3 : Optimized Chromatogram of SITA and MET**

**Table-1 Optimized Chromatographic Condition of SITA and MET**

| | |
|---|---|
| **Stationary Phase** | Chromasol ONYX CN (4.6mm×250mm);10µm |
| **Elution Mode** | Isocratic |
| **Mobile Phase** | Buffer: Acetonitrile (90:10v/v) |
| **Diluent** | Diluent 1- 0.1% OPA:ACN (95:5v/v)<br>Diluent 2- Water |
| **Flow Rate** | 1.0ml / min |
| **Detection wavelength** | Sitagliptin 205nm<br>Metformin Hydrochloride 232nm |
| **Injection Volume** | 10µL |
| **Column temperature** | 30°C |
| **Run Time** | 15 mins |

**Assay**

Assay of tablet formulation containing 50mg of Sitagliptin and 1000mg of Metformin and Six injections of above prepared sample and standard solutions were injected. The assay of the sample was calculated by comparing the areas of standard and sample peaks. The assay of formulation found within limit.

## IV. METHOD VALIDATION

The validation of RP-HPLC method For the determination of Sitagliptin and Metformin HCl as per the protocol and to demonstrate that the method Is appropriate for its intended use was studied for the Following parameters. All the validation parameters were carried out according to ICH.

The parameters assessed were Specificity (Blank / Placebo Interference, Forced degradation studies), Linearity, Method Precision (Repeatability), Intermediate Precision (Ruggedness), Accuracy, Robustness.

**Specificity**

**Blank/ Placebo Interference**

Examine the blank and Placebo Interference at the retention time of main peak retention time.

**Forced degradation studies**

Forced degradation studies were performed on SITA and MET to prove the stability- indicating property of the Method. The stress conditions employed for degradation study of SIT and MET include Acid hydrolysis (0.1 M HCl), Base hydrolysis (0.1M NaoH), Thermal (105°C) and Humidity (90%RH) degradation. For Acid, Base the monitoring period was 1hr whereas for Thermal and Humidity it was 24 hrs. Peak purity of the principal peak in the chromatogram of stressed samples of SITA and MET tablets was checked using PDA detector.

**Linearity**

The linearity of this method was investigated by using the concentrations 80, 90, 100, 110, 120% of both drugs. These concentrations were prepared by diluting appropriate volume of Working standard diluents. Calibration curve of Sitagliptin and Metformin HCl were constructed by plotting concentration vs. peak areas, and the Regression equations were calculated.

**Method Precision (Repeatability)**

Method precision was studied by injecting six sample preparation of the assay on the single batch of the drug product as per the methodology. Calculating the Percentage of relative standard deviation (%RSD) for six determinations of peak areas of SITA and MET.

**Intermediate Precision (Ruggedness)**

Ruggedness according to the USP, is the degree of reproducibility of the results obtained under a Variety of conditions, expressed as % relative standard deviation (RSD). These conditions include differences in analyst, instruments, days and experimental periods.

**Accuracy**

The accuracy was carried out by adding known amounts of each analyte corresponding to three Concentration levels (50, 100 and 150%) of the Labeled claim to the excipients. At each level, three determinations were performed and the accuracy Results were expressed as percent of amount recovered By the proposed method.

**Robustness Study**

Robustness of the method was demonstrated by deliberately changing the chromatographic conditions. The flow rate of the mobile phase was changed from rate (1.0 ml/min of set value i.e. 0.9 ml/min and 1.1 ml/min) and variation of Temperature (30°C set value i.e. 25°C and 30°C) and changed the wavelength (Sita 205nm set value i.e. 200nm and 210nm, Met 232nm set value i.e. 227nm and 237nm).

## V. RESULTS AND DISCUSSION

**Specificity**

**Blank/Placebo Interference**

No Interference at Retention time for main peaks. It demonstrates that the absence of interference from other materials in the pharmaceutical formulations and therefore confirm the specificity of the proposed method (Table 2).

**Table 2: Specificity Blank/Placebo Interference Result**

| SAMPLE ID | RETENTION TIME | INTERFERENCE AT SITA/ MET |
|---|---|---|
| **Blank** | No peaks observed at retention time of principle peaks | Nil |
| **Placebo** | No peaks observed at retention time of principle peaks | Nil |

**Table 3: Specificity – Retention Time**

| COMPONENT NAME | RETENTION TIME (STANDARD) | RETENTION TIME (SAMPLE) |
|---|---|---|
| **Metformin HCl** | 2.663 mins | 2.663 mins |
| **Sitagliptin** | 7.802 | 7.790 mins |

**Table 4: Specificity – Peak Purity Results**

| COMPONENT NAME | PEAK PURITY | | | |
|---|---|---|---|---|
| | STANDARD | | SAMPLE | |
| | PEAK PURITY INDEX | SINGLE POINT THRESHOLD | PEAK PURITY INDEX | SINGLE POINT THRESHOLD |
| **Metformin Hcl** | 1.000000 | 0.999940 | 1.000000 | 0.999999 |
| **Sitagliptin** | 0.999999 | 0.674999 | 0.999998 | 0.990528 |

**Table 5: Forced degradation study data**

| DEGRADATION CONDITIONS | % DEGRADATION OF SITA | % DEGRADATION OF MET |
|---|---|---|
| **Acid (0.1M HCL)** | 9.6 | 1.1 |
| **Base (0.1M NaoH)** | 10.9 | 2.4 |
| **Thermal (105°C)** | 0.5 | 0.4 |
| **Humidity (90%RH)** | 1.2 | 0 |

**Linearity**

Linearity was good in the concentration range of Sitagliptin standard as 5-7.5 µg/ml and Metformin HCl Standard as 80 – 120 µg/ml for respectively. The correlation coefficient was found 1.000 for SITA and 0.9999 for MET. The results shown that within the concentration range Indicated there was an excellent correlation between peak area ratio and each concentration of the sitagliptin and Metformin HCl.

**Table 6: Linearity**

| SR.NO | SITA | | | MET | | |
|---|---|---|---|---|---|---|
| | Conc. in ppm | Area | Correlation coefficient | Conc. in ppm | Area | Correlation coefficient |
| 1 | 5.0 | 115128 | | 80.3 | 3817456 | |
| 2 | 5.6 | 114010 | | 90.4 | 3817721 | |
| 3 | 6.3 | 115311 | 1.000 | 100.4 | 3810392 | 0.9999 |
| 4 | 6.9 | 114621 | | 101.4 | 3810373 | |
| 5 | 7.5 | 115208 | | 102.5 | 3818534 | |

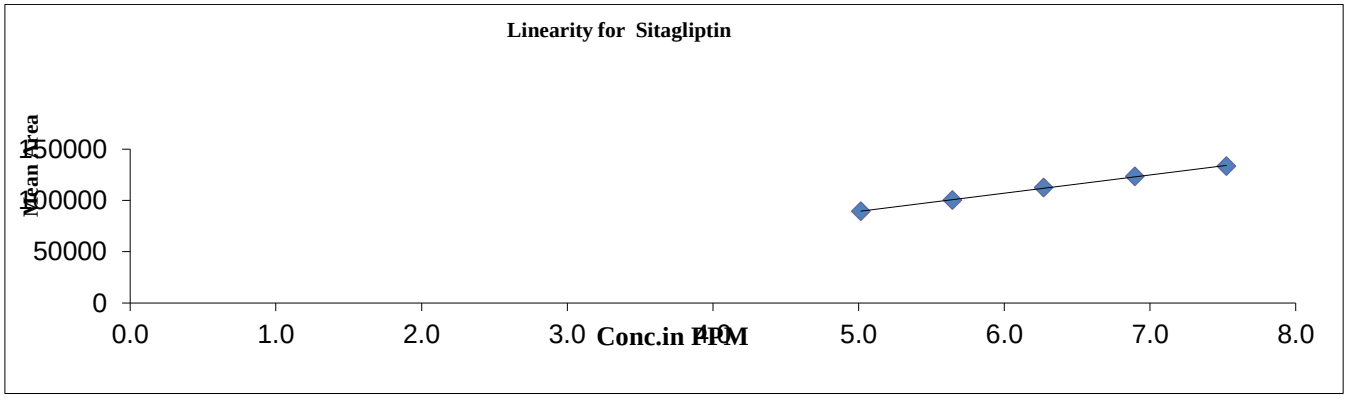



**Fig 4 : Linearity Plot For SITA**

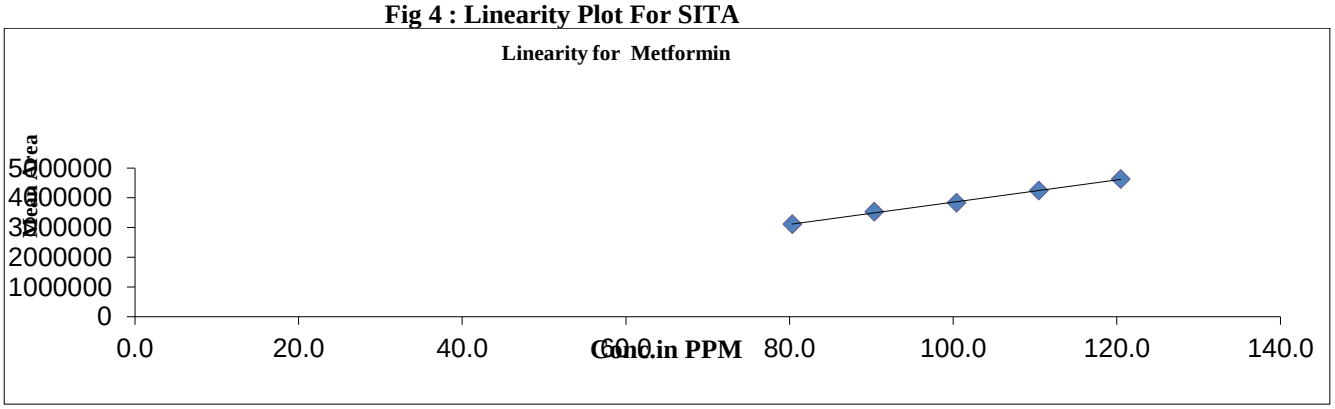



**Fig 5: Linearity Plot For MET**

**Method Precision (Repeatability)**

Method Precision was established by determining the %RSD for six determination of Assay.

**Table 7: Method Precision (Repeatability)**

| SAMPLE NO | % ASSAY | |
|---|---|---|
| | SITA | MET |
| Sample 1 | 100.5 | 100.1 |
| Sample 2 | 98.7 | 98.3 |
| Sample 3 | 100.2 | 99.9 |
| Sample 4 | 98.8 | 98.3 |
| Sample 5 | 100.3 | 99.5 |
| Sample 6 | 100.1 | 98.6 |
| **Mean**<br>**Standard Deviation(SD)**<br>**%RSD**<br>**95% Confidence interval** | **99.8**<br>**0.7999**<br>**0.8**<br>**0.6** | **99.1**<br>**0.816**<br>**0.8**<br>**0.7** |

**Intermediate Precision (Ruggedness)**

Intermediate precision was established by determining the overall %RSD for (intra-day and inter-day) method precision and Intermediate Precision for assay.

**Table 8: Intermediate Precision (Ruggedness)**

| SAMPLE ID | % ASSAY (Repeatability) | | % ASSAY (Ruggedness) | |
|---|---|---|---|---|
| | SITA | MET | SITA | MET |
| Sample 1 | 100.5 | 100.1 | 98.5 | 101.1 |
| Sample 2 | 98.7 | 98.3 | 97.9 | 101.0 |
| Sample 3 | 100.2 | 99.9 | 99.8 | 101.3 |
| Sample 4 | 98.8 | 98.3 | 99.2 | 101.1 |
| Sample 5 | 100.3 | 99.5 | 98.3 | 101.0 |
| Sample 6 | 100.1 | 98.6 | 98.6 | 101.0 |
| **Mean**<br>**Standard Deviation(SD)**<br>**%RSD**<br>**95% Confidence interval** | **99.8**<br>**0.799**<br>**0.8**<br>**0.6** | **99.1**<br>**0.816**<br>**0.8**<br>**0.7** | **98.7**<br>**0.679**<br>**0.7**<br>**0.5** | **101.1**<br>**0.117**<br>**0.1**<br>**0.1** |
| **Overall Avg (n= 12)** | SITA 99.2% | | MET 100% | |
| **SD (n=12)** | SITA 0.895 | | MET 1.134 | |
| **%RSD (n=12)** | SITA 0.902 | | MET 1.134 | |

**Accuracy Study**

The % mean recovery obtained for SITA and MET was 99.7% and 101.1%respectively. The %RSD Is less than 2. Recoveries of Sitagliptin and Metformin HCl were in between 98% - 102%. This is in accordance with ICH guidelines. Therefore method was found to be accurate.

**Table 9: Accuracy Study**

| ACCURACY LEVEL | AMOUNT ADDED (ppm) | | AMOUNT RECOVERED (ppm) | | % RECOVERY | |
|---|---|---|---|---|---|---|
| | SITA | MET | SITA | MET | SITA | MET |
| 50% Level Sample - 1 | 3.13 | 49.78 | 3.17 | 50.32 | **101.1** | **101.1** |
| 50% Level Sample - 2 | 3.13 | 49.78 | 3.18 | 50.29 | **101.7** | **101.0** |

| | | | | | | |
|---|---|---|---|---|---|---|
| 50% Level Sample - 3 | 3.13 | 49.78 | 3.12 | 50.23 | **99.9** | **100.9** |
| 100% Level Sample - 1 | 6.26 | 99.56 | 6.17 | 101.08 | **98.6** | **101.5** |
| 100% Level Sample - 2 | 6.25 | 99.56 | 6.19 | 100.87 | **99.1** | **101.3** |
| 100% Level Sample - 3 | 6.25 | 99.56 | 6.32 | 100.79 | **101.1** | **101.2** |
| 150% Level Sample - 1 | 9.38 | 149.34 | 9.20 | 150.89 | **98.1** | **101.0** |
| 150% Level Sample - 2 | 9.38 | 149.34 | 9.32 | 150.44 | **99.4** | **100.7** |
| 150% Level Sample - 3 | 9.38 | 149.34 | 9.26 | 150.66 | **98.7** | **100.9** |
| **Overall Mean** | | | | | **99.7** | **101.1** |
| **Standard Deviation** | | | | | **1.3** | **0.2** |
| **%RSD** | | | | | **1.3** | **0.2** |

**Robustness Study**

There was no significant change in the peak areas and retention times of SITA and MET when the flow rate was varied by ±0.1ml, Temperature was varied by ±5°C and the wavelength was varied by ±5nm.all analytes were adequately resolved.

## VI. CONCLUSION

A simple, selective, sensitive and stability indicating RP-HPLC analysis method was developed for the simultaneous estimation of Sitagliptin and Metformin HCl in Pharmaceutical Oral Solid Dosage formulation. The method was found economical and simple with involvement of few steps. The assay has been validated as per the ICH guideline and the results have shown that the method is sensitive, accurate and reproducible. Therefore, the developed method is found suitable for the simultaneous determination of sitagliptin and metformin in formulations. In combination drugs. This method is suitable for Routine analysis and quality control of pharmaceuticals.

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