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DOE-Driven RP-HPLC Method Development and Validation for Rapid Estimation of Lobeglitazone

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ABSTRACT:

Background: The study aims to integrate the Experiment Planning (DOE) methodologies with High-Performance Liquid Chromatography in the Reverse Phase (RP-HPLC) for the development of an analytical method to estimate lobeglitazone.

Methods: A DOE strategy was applied to maximize critical method parameters for RP-HPLC, including mobile phase composition, flow rate, and column temperature. The method development was carried out using an analytical column Inspire with a C18 (150 × 4.6 mm,5 µm). stationary phase and acetonitrile-containing mobile phase and potassium dihydrogen phosphate the procedure showed exceptional linearity range at wavelength of 240nm with a correlation coefficient (R^2) of 0.999. The method was validated according to ICH guidelines, showing satisfactory results in terms of specificity, sensitivity, repeatability, and robustness.

Results: The enhanced RP-HPLC technique demonstrated high precision and accuracy in the estimation of lobeglitazone. The DOE approach enabled systematic optimization, resulting in a robust method with improved sensitivity and reduced analysis time.

Conclusion: The integration of with DOE in RP-HPLC method development offers a strategic approach to enhance analytical method performance. This study successfully established a reliable and efficient RP-HPLC technique for determining lobeglitazone, which can be potentially applied in quality control and pharmacokinetic studies.

Keywords: lobeglitazone, Design of Experiments, RP-HPLC, Method Development, Anti diabetic Drug. T2DM also known as type 2 diabetes,

INTRODUCTION:

Type 2 diabetes mellitus (T2DM) is a chronic progressive metabolic disease characterized by insulin resistance and β -cell dysfunction.[1] because the Pathophysiology of T2DM is complex and multifactorial, a variety of oral anti -diabetic agents have developed based on the underlying mechanisms associated with T2DMOne of the classes of OADS that has been developed thus far is the thiazolidines class [2]. TZDSs increases insulin sensitivity by activating peroxisome proliferator- activated receptor (PPAR). The main TZD endorsed for TZDM was troglitazone, which was removed from the market 2000 in light of hepatotoxicity. [3] Other TZDS rosiglitazone and pioglitazone, were approved by the U.S. Food and drug administration in 1999 and due to their potent glycemic durability, they have been widely used for T2DM treatment. Lobeglitazone was at first developed by chon Kun Darn Drugs in Korea to treat diabetes on July 4, 2.13, the service of food and medication wellbeing (Korea) supported by lobeglitazone, i.e., the Drugs under brand name Duvie. [4] Duvie is presented as an oral tablet that contain 0.5 mg of free lobeglitazone. The recommended dosage is 0.5 mg every 5 days. Because of the high prevalence of insulin resistance in India, Glenmark Pharmaceuticals Limited was the first type 2 diabetes treatment company to introduce lobeglitazone to the country. The medication, which is sold under the brand name LOBG and must be taken orally by patients once daily, contains lobeglitazone (0.5 mg) [6],[7]. It is prescribed to patients with insulin resistance to improve glycemic control. According to the FDA reports, Glenmark recently got endorsement from drugs controller, the medication control directorate general of India (DCGI), to make and market [8] [10] lobeglitazone in view of randomized twofold - tie preliminary in stage 3 patients/individual matured 18yrs, and over who had type 2 diabetes. Insulin opposition is a chemical made by your pancreas that behaves like a key to allow blood to sugar in to the cells in to your body for use energy. On the off chance that you have type 2 diabetes cells don't answer regularly to insulin. The term for this is insulin resistance. High blood sugar is bad for the body and can cause kidney disease, heart disease, vision loss, and other serious health issues.

SYMPTOMS: Increases thirst, frequent urination, Increased hunger, Unintended Weight loss, Blurred Vision, Fatigue

DRUG PROFILE:

Lobeglitazone is an antidiabetic medication from the thiazolidine class of drugs. it essentially capability as an insulin sensitizer by proliferator by restricting and enacting peroxisome proliferator-initiated Receptors (PPAR) gamma inside fat cells. [10] By enacting PPAR-gamma and advancing the limiting of insulin at fat cells, [11] lobeglitazone accordingly has been displayed to decrease glucose levels, lower hemoglobin A1C (HB1C) levels and further develop lipid and liver profiles. dissimilar to pioglitazone, which is a double PPAR agonist at PPAR - alpha and PPAR - gamma, Lobeglitazone is an unadulterated Standard alpha agonist. Lobeglitazone was created by presenting a P-methoxy phenoxy bunch at the fourth place of pyramid bunch in the

rosiglitazone structure. Lobeglitazone has a higher binding affinity than pioglitazone and rosiglitazone [12, 13].

Lobeglitazone has well -tolerated anti -diabetic therapy in healthy females. Lobeglitazone is a novel thiazolidine agent with similar glycemic efficacy that reduces insulin resistance. Lobeglitazone decreased the gamble of cardiovascular complications. [14] Lobeglitazone was endorsed by the Service of Food and Wellbeing (South Korea) in 2013, and is being checked by post advertising observation until 2019. Lobeglitazone isn't supported for use by either the Food and Medication Organization (USA) Wellbeing Canada, or European Drugs Office Enemy use in the administration of diabetes.

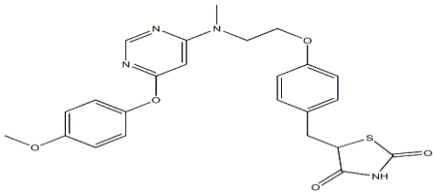


Figure no: 1. structure of Lobeglitazone

This research presents a novel approach to estimate lobeglitazone using a design of experiment (DOE). RP-HPLX method. Design of Experimental is a method of statistical analysis that allows researchers to optimize experimental parameters systematically, leading to more efficient analytical method. Lobeglitazone is a pharmacophore which has 2,4 thiazolidinedione bunch with an ethyl-benzyl N-methyl amino gathering bound to this as an interfacing join. Its chemical name is5-[4-(2-[6-(-4-Methoxy-phenoxy)-pyrimidine-4-y1-methyl-amino-ethoxy)-benzyl] thiazolidine-2,4-dione hydrosulphuric acid, and its structural formula is C24H24N4O5S. The lobeglitazone and PPAR co-crystal structure the structure of lobeglitazone was altered to include a P-methoxy phenoxy group at the fourth position of the pyrimidine moiety [17, 18]. The literature review revealed that a few logical strategies have been accounted for lobeglitazone in RP-HPLC individually and in combination. This present study reports simultaneous estimation of lobeglitazone.

1.To use the DOE approach to systematically assess and optimize important variables the impact the HPLC analysis, such as the injection volume, temperature, column, flow rate, and composition of mobile phase.

2.Creating an RP-HPLC technique with increased sensitivity and accuracy for lobeglitazone based on DOE.

3. lobeglitazone analytical method of estimation will be developed by RP-HPLC method by optimizing the chromatographic conditions.

4.The developed method is validated according to ICH guidelines for various parameters specified in ICH guidelines, Q2 (R1)

5.The significance of this research lies in its potential to provide a more sensitive and efficient HPLC method for the estimation lobeglitazone thus contributing to the quality control of this drug. Additionally, the utilization of design of experiment principals ensures a systematic and thorough exploration of experimental space.

Experimental Methods:

RP-HPLC Method Development:

Chemicals and reagents: Lobeglitazone is antidiabetic developed by Glenmark pharmaceuticals and sold as part of the brand name LOBG, Potassium dihydrogen Phosphate and acetonitrile serves as a portable phase.

Instrumentation: Waters collusion fluid chromatography (model 2695) observed with enable 2.0 information taking care of framework and a locator of PDA was utilized for this review.

Method optimization: Initially, different pH combinations and quantities of methanol, ammonium acetate buffer, and methanol, phosphate buffer were explored as the mobile phase. Lastly, the mobile phase was adjusted so as to Acetonitrile with Potassium dihydrogen phosphate (pH 3.0), in proportion 70: 30 v/v respectively. lobeglitazone was detected by scanning in the 200–400 nm region in methanol diluents. from the chosen wavelength of 240 nm in the UV spectrum. This wavelength exhibits good absorption for both medications. The dose form of lobeglitazone was estimated using the established HPLC method.

Preparation of buffer and mobile phase:

Preparation of potassium dihydrogen phosphate buffer: Weigh 6.8 grams of potassium dihydrogen phosphate and taken in to a 1000ml beaker was taken in a 1000 ml of H20 dissolved and diluted adjusted the pH with OPA and membrane filtration with 0.45 µm. and the volume was obtained.

Preparation of Lobeglitazone sample solution: Take 50 mg of sample was taken and dissolved it in methanol and make up the volume at 50 ml and ultra sonicated for 20 min and filtered by using microfiltration (Stock –A). From this stock-A 1 ml of solution is withdrawn and dissolved in 10 ml of methanol it is working solution. Then it is filtered through 0.44-micron Injection filter. (Stock solution of lobeglitazone Sample)

Design of Experiment [19]: The drug sample of Lobeglitazone was subjected to the design of experiment process. Box-Behnken response surface design was employed to identify the underlying facts of effects of factors and their interaction effects on selected method responses. A total of 17 runs were conducted.

Statistical analysis:

❖ By using ANOVA, the statistical calculations were processed for variables screening and optimization of the method the statistical tools provide the numerical verification of variables and its effect on responses.

Method operable design region: The space known as Design space is created by the many combinations and reciprocities of input elements**.** The Sigma Tech software's contour graphs were used to establish the design space.

Method Verification: The software suggested the optimal method circumstances to accomplish the intended method objectives. The method was verified to check the predictability of the proposed model.

METHOD VALIDATION: [20-22]

1. Linearity:

From the above standard stock solution pipette out 0.1, 0.2, 0.3, 0.4 and 0.5 ml into a five 10ml volumetric flask and made up to the volume 10ml with diluent to get 1 to 10µg/ml concentrated solutions of lobeglitazone was filtered and injected into HPLC system and peak area was measured. Plotted a graph of peak area between and concentration. Correlation coefficient was determined by regression analysis.

2. Precision:

From the standard stock solution an aliquot of 0.6ml was added into a six 10ml volumetric flasks, made up to 10 ml with a diluent. Later it was filtered and six replicates were injected into HPLC system and measured the area for all six injections.

3. Accuracy:

Preparation of standard stock solution: 1000µg/ml of standard stock solution was prepared. Further pipette out 0.6ml of Standard stock solution into 10 ml volumetric flask and was diluted with diluent up to the mark.

Preparation of sample solution:

Accuracy solutions at 50% level: Sample 5 mg is weighed, and then transferred to a 10 ml volumetric flask. About Diluent of 7 ml is added likewise, the sample is sonicated to dissolve it completely and bring the volume up to the required level. The sample was then injected into an HPLC injector after 0.6 ml of the aforesaid stock solution was pipetted out into a 10 ml volumetric flask and the volume was adjusted with diluents.

Accuracy solutions at 100% level: Sample 10 mg is weighed, then transferred to a 10 ml volumetric flask. 2 ml of diluent is added, and the sample is sonicated to dissolve it completely and bring the volume up to the required level. 0.6 ml of the aforesaid stock solution was pipetted out again into a 10 ml volumetric flask, the volume was adjusted with diluent, and the sample was then injected into an HPLC injector.

Accuracy solutions at 150% level: After measuring and transferring 15 mg of the sample into a 10 ml volumetric flask, 2 ml of diluent is added, and the sample is sonicated to dissolve it entirely and bring the volume up to the required level. Subsequent to adding diluent to bring the volume sufficient, pipette out an extra 0.6 ml of the previously mentioned stock arrangement into a 10 ml volumetric flagon and infuse the example into the HPLC injector.

LOD and LOQ:

The limit of detection and limit of quantification was calculated based on the standard deviation of the response and slope of calibration curve.

Results and discussion:

Table no: 1 Box – Behnken design experimental runs

Std	Run	Factor 1 A: buffer	Factor 2 B: ph.	Factor 3 C: flow rate	Response 1 R1	Response 2 R2
13	1	50.00	3.50	1.25	2.951	4312.12
2	2	50.00	3.00	1.25	3.018	5596.36
1	3	50.00	3.00	1.25	2.99	5348.18
7	4	50.00	3.50	1.50	2.952	4313.13
8	5	50.00	3.50	1.50	2.952	4313.13
17	6	50.00	3.50	1.25	2.953	4313.14
16	7	50.00	3.50	1.25	2.953	4315.14
10	8	50.00	4.00	1.00	2.954	4315.23
14	9	50.00	3.50	1.25	2.951	4315.26
4	10	50.00	4.00	1.25	2.962	4315.28
9	11	50.00	3.00	1.00	2.978	5413.99
15	12	50.00	3.50	1.25	2.953	4315.29
11	13	50.00	3.00	1.50	2.973	5432.87
5	14	50.00	3.50	1.00	2.974	4315.30
6	15	50.00	3.50	1.00	2.974	4315.30
12	16	50.00	4.00	1.50	2.975	4315.31
3	17	50.00	4.00	1.25	2.976	4315.32

Surface Graph: Retention time

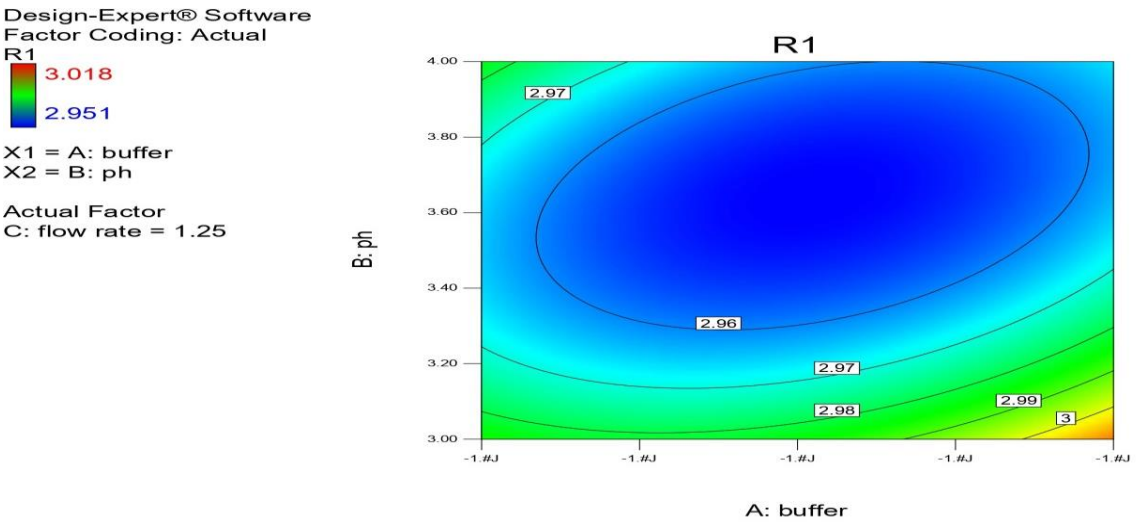


Figure no :2 Retention time

Surface curve Graph: Theoretical plates

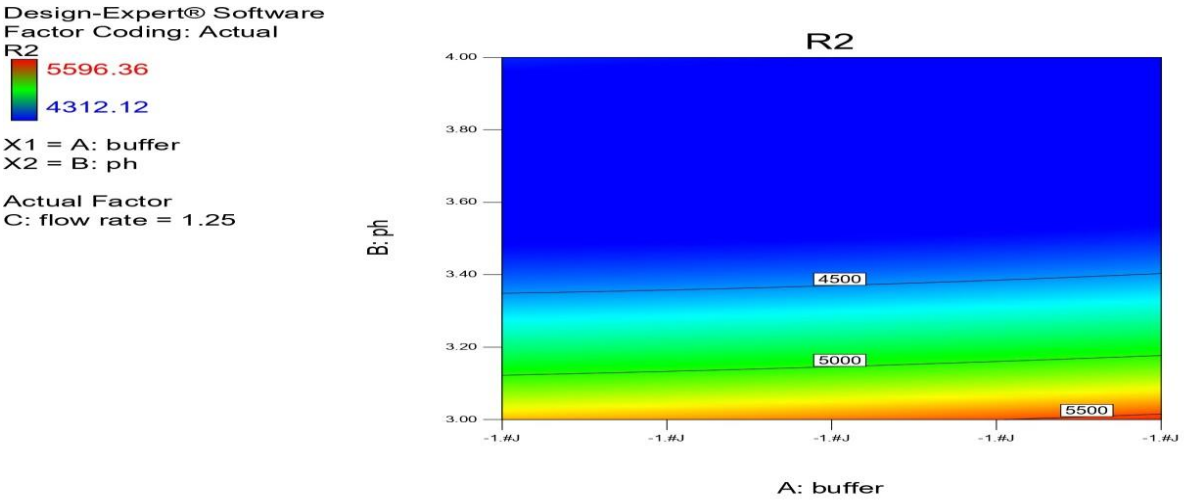
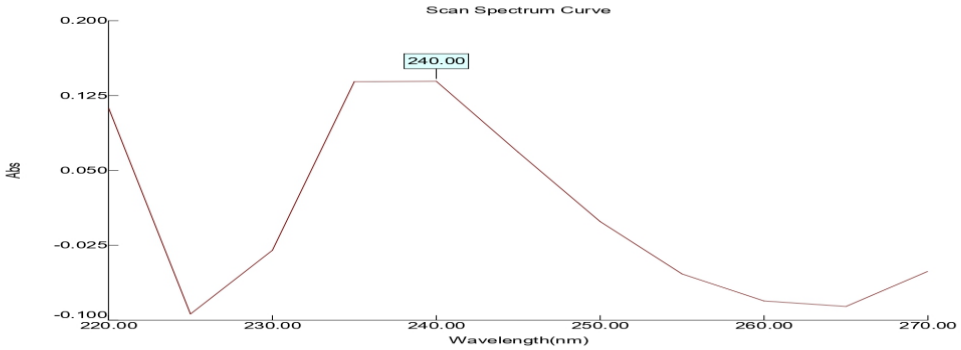


Figure no: 3 - Theoretical plates

Method development

Determination of detection wavelength in mobile phase:



- **Instrument Performance**
  Model : UV-VIS Spectrophotometer
  Number : 30-1885-01-0091
  Spectral Bandwidth : 2.00 nm
- **Scan Spectrum Performance**
  Scan Range : 220.00 to 270.00 nm
  Measure Mode : Abs
  Interval : 5.00 nm
  Speed : Medium
  Data File : Untitled1.spd
  Create Date/Time : 25 April 2024 14:32:09
  Data Type : Original
  Method File:
- **Analyse Note**
  Analyser : Administrator
  Sample Name : Blank
  Comment :

No.	P/V	Wavelength(nm)	Abs	Comment
1	Peak	270.00	-0.051	
2	Peak	240.00	0.139	

Figure no: 4 Wavelength of lobeglitazone

Validation parameters

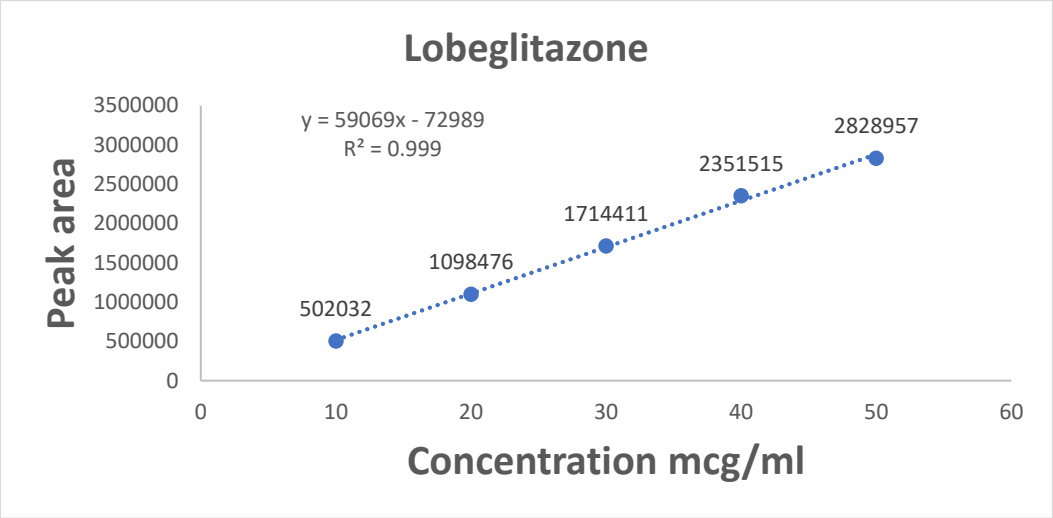
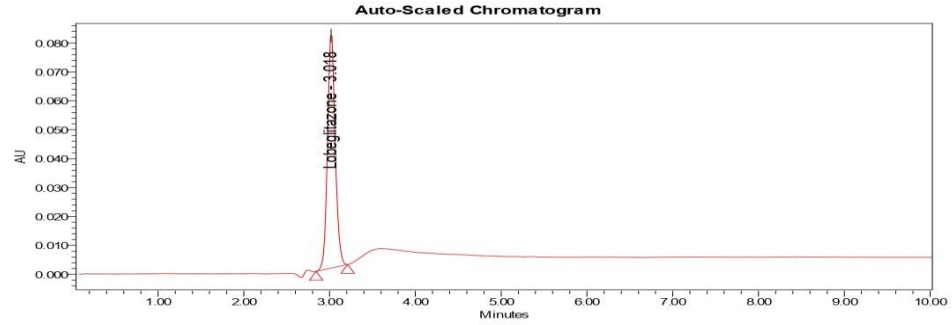


Figure no: 5 Linearity graph of lobeglitazone

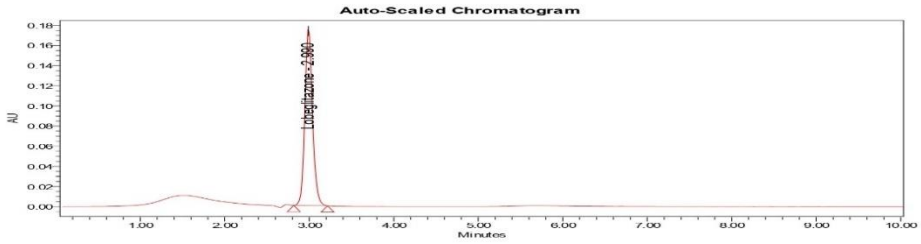
S. No	**Linearity Level**	**Concentration**	**Area**
1	I	10	502032
2	II	20	1098476
3	III	30	1714411
4	IV	40	2351515
5	V	50	2828957
Correlation Coefficient			**0.999**

Table no: 2 linearity concentration data

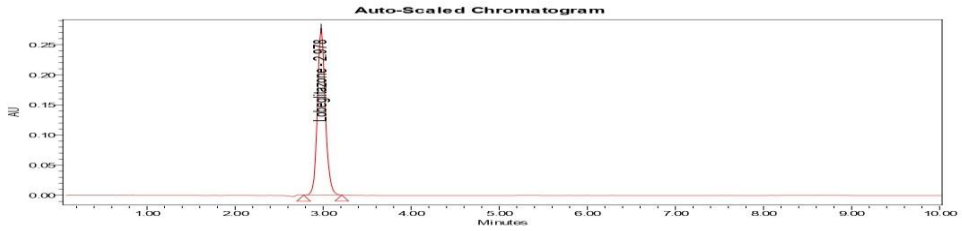
Linearity: 1



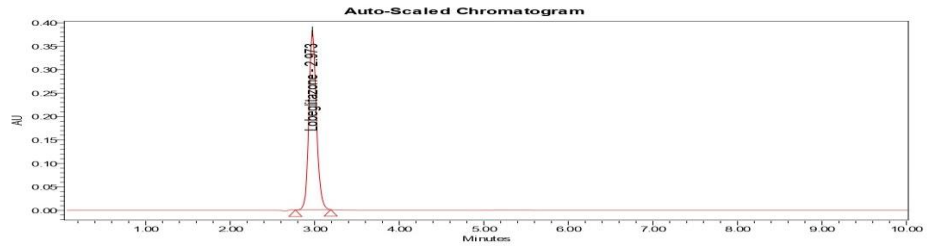
Linearity :2



Linearity:3



Linearity: 4



Linearity: 5

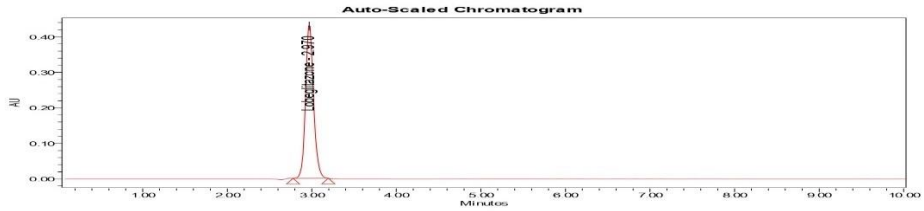


Figure no: - 7 Linearity graphs

Peak Results

Name: Lobeglitazone

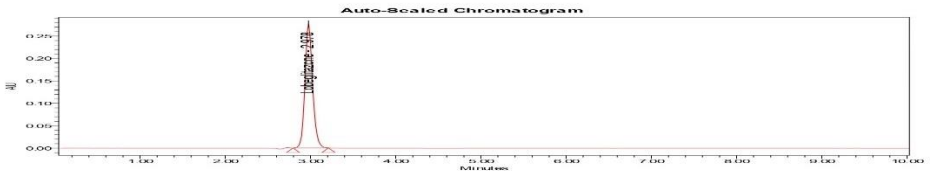
	Sample Name	Name	RT	Area	Height	USP Plate count	USP Tailing
1	Linearity -1	Lobeglitazone	3018	502032	81212	5596.36	1.08
2	Linearity-2	Lobeglitazone	2990	1098476	175229	5348.18	1.14
3	Linearity -3	Lobeglitazone	2978	1714411	274855	5413.99	1.14
4	Linearity-4	Lobeglitazone	2973	2351515	379686	5432.87	1.14
5	Linearity-5	Lobeglitazone	2970	2828957	434026	4815.47	1.14

Table no: 3 linearity data

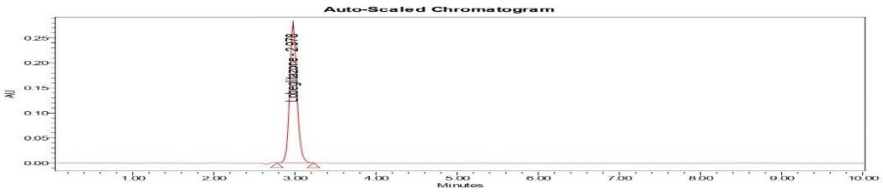
2. precision

Table no : 4 Precision data

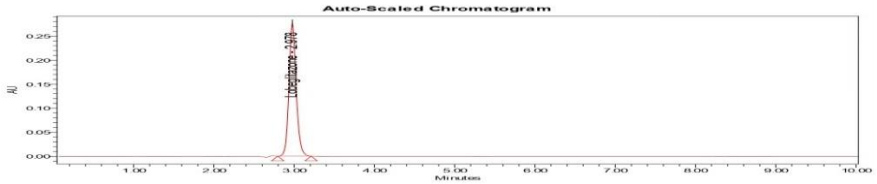
	Name	RT	Area	Height	USP Plate Count	USP Tailing
1	Lobeglitazone	2.978	1714738	274871	5413.47	1.14
2	Lobeglitazone	2.978	1716576	274929	5411.33	1.14
3	Lobeglitazone	2.978	1710915	274725	5418.63	1.13
4	Lobeglitazone	2.978	1715938	274861	5413.22	1.14
5	Lobeglitazone	2.978	1696553	274053	5440.47	1.14
6	Lobeglitazone	2.978	1714738	274871	5413.47	1.14
Mean			1711576.3			
Std Dev			7617.7			
% RSD						



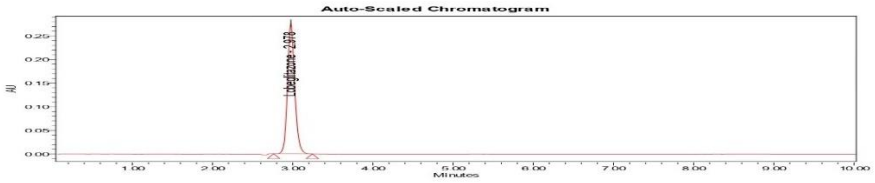
First injection of precision



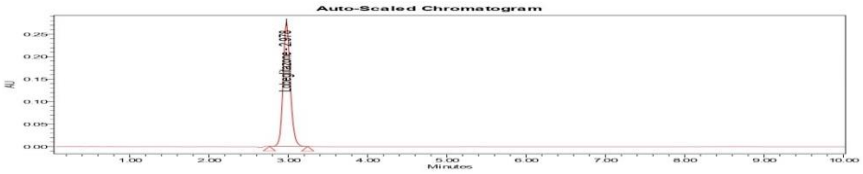
Second injection of precision



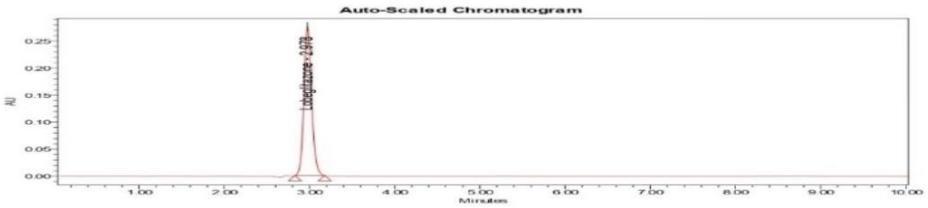
Third injection of precision



Fourth injection precision



Fifth injection of precision



Sixth injection of precision

Figure no: 8 precision graphs

3. Accuracy

i) Accuracy -50%

Table no:5 Accuracy 50% data

	Name	RT	Area	Height	USP Tailing	USP Plate count
1	Lobeglitazone	3.018	498883	80982	1.06	5630.01
2	Lobeglitazone	3.018	498883	80982	1.06	5630.01
3	Lobeglitazone	3.018	500349	81076	1.07	5612.34

Mean			499371.6			

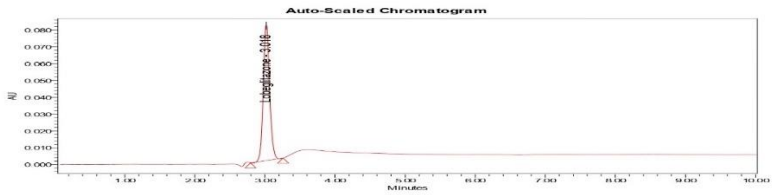


Figure no:9 Accuracy data 50 %

Table no:6 Accuracy data 100 %

	Name	RT	Area	Height	USP Tailing	USP Plate Count
1	Lobeglitazone	2.978	1712421	274742	1.14	5417.47
2	Lobeglitazone	2.978	1716576	274929	1.14	5411.33
3	Lobeglitazone	2.978	1708661	274621	1.14	5421.86
Mean			1712552.4			

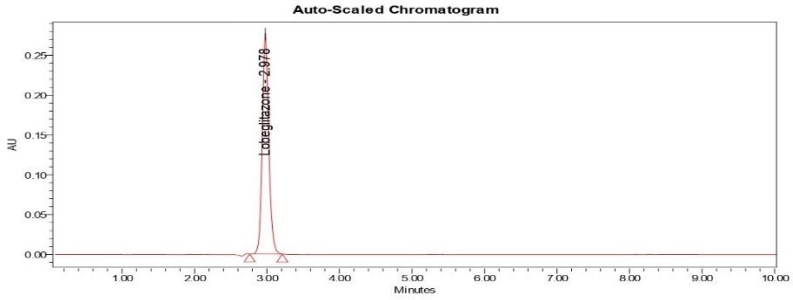


Figure no: 10 Accuracy 100% data

Accuracy - 150%

Table no: 7 Accuracy 150% data

	Name	RT	Area	Height	USP Tailing	USP Plate Count
1	Lobeglitazone	2.970	2834518	434163	1.14	4811.74
2	Lobeglitazone	2.970	2839147	434353	1.14	4807.53
3	Lobeglitazone	2.970	2838824	434295	1.15	4808.55
Mean			2837496.1			

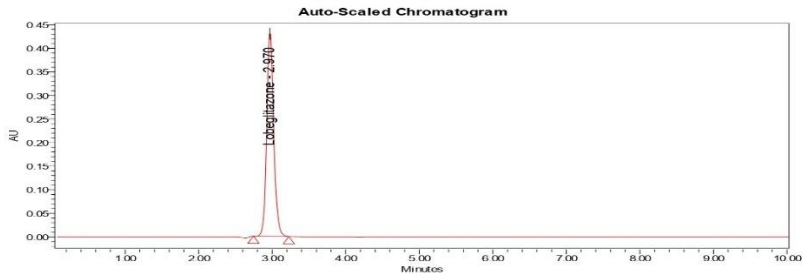


Figure no:11 Accuracy -150 % data

Conclusion:

The study focuses on the lobeglitazone exhibits a long-term safety profile and effective in glycemic control. Further the physio-chemical properties of lobeglitazone having hydrophobic interactions there is a consideration for using non polar or less polar solvents such as Acetonitrile or Methanol as a part of mobile phase. Based on polar interactions the Mobile phase should also include polar solvents such as having ionizable hydrogen for example formic acid or Ortho phosphoric acid. Optimization of pH, sensitivity to improve Retention time and Resolution. so hence, mobile phase consisting of water with potassium dihydrogen phosphate is suggested based on the ionizable groups showing slightly acidic conditions can optimize the mobile phase pH at around 3.

The developed RP-HPLC method has demonstrated excellent performance characteristics, including high sensitivity, reproducibility, and a reduced analysis time, making it suitable for routine analysis and quality control of lobeglitazone in pharmaceutical formulations. Additionally, the integration of computational and experimental approaches exemplifies a powerful strategy for method development, potentially applicable to other analytical difficulties with pharmaceutical analysis

The findings of this research highlight the RP-HPLC and DOE techniques in analytical method development, offering a comprehensive framework that can enhance the efficiency and reliability of chromatographic methods. Future research could explore the application of this integrated approach to other compounds and extend its use to various types of chromatography and analytical techniques.

In conclusion, the integration of with DOE in RP-HPLC method development represents a significant advancement in analytical chemistry, providing a powerful estimation tool for lobeglitazone and offering a model for the development of other analytical methods in the pharmaceutical field.

The Design of Experiment was carried out by using the Box-Behnken design & the assessment of independent variables. A rapid, novel, precise cost effective & robust RP-HPLC method for lobeglitazone estimation in bulk and dosage form was developed be a more deliberate factor for method optimization, according to response surface plots. The use of DOE approach is a flexible strategy for reducing the no. of trial experimental runs required for a method to be created in a

short period of time. The proposed method was found to be rapid, accurate, precise, specific, robust, rugged and economical.

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