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A QUALITY BY DESIGN (QBD) ASSISTED RP-HPLC METHOD DEVELOPMENT AND VALIDATION FOR THE SIMULTANEOUS ESTIMATION OF LINAGLIPTIN AND DAPAGLIFLOZIN PROPANEDIOL MONOHYDRATE IN TABLET DOSAGE FORM

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Linagliptin, Dapagliflozin Propanediol Monohydrate, QbD, RP-HPLC,Validation.

ABSTRACT:

Objective: Linagliptin and Dapagliflozin Propanediol Monohydrate in tablet formulations were successfully isolated and measured using a rapid, precise, sensitive, and reliable RP-HPLC technique. The optimization process makes use of a Quality by Design (QbD) methodology.The separation of chromatogram was performed with a JASCO HPLC (model PU2075 Plus) with a UV-200 Plus detector. A Qualisil 5 BDS C8 (250 × 4.6mm, 5 µm particle size) column were used in isocratic conditions. The Mobile phase is used in ratio of 50:50%v/v (ACN: OPA) and pH was adjusted to 3.5 using Triethylamine 1.0ml/mim will be the flow rate, 20ul will be a injection volume and 230nm is a Wavelength, resulting 8min will be the total run time.Linagliptin's retention duration was 2.783 minutes, were as Dapagliflozin Propanediol Monohydrate's was 4.925 minutes. Linagliptin as well as dapagliflozin propanediol monohydrate have linearity ranges of 5,10,15,20 and 25µg/ml and 10,20,30,40 and 50µg/ml, respectively, with correlation coefficients (r^2) of 0.9994 and 0.9991. For both drugs, the percentage recovery varied between 99.92% and 99.98%. The drug contents were 99.9% w/w for linagliptin and 99.91% w/w for dapagliflozin propanediol monohydrate, according to the assay results. With intraday or interday precision showing an average relative standard deviation (%RSD) of less than 2%, the approach demonstrated good reproducibility. The method's robustness evaluation shows that it is unaffected by even minor variations in the chromatographic settings.In conclusion, this QbD-assisted RP-HPLC method is straightforward, highly specific, rapid, and trustworthy, making it appropriate for routine quality control assessments.

INTRODUCTION:

Linagliptin a medication that belongs to the dipeptidyl peptidase-4 inhibitor class.[1] Empirical formula of

Linagliptin is (C25H26N802). This compound's reversible and competitive inhibition of the DPP4 enzyme prolongs the action of incretin hormones such as glucagon-like peptide-1 and dependent on glucose insulinotropic polypeptide, which increase insulin secretion from pancreatic beta cells while decreasing glucagon release from alpha cells. Empirical formula of Dapagliflozin Propanediol Monohydrate is (C21H25ClO6.C3H8O2.H2O)[2-4] The sodium salt derivative of dabigatran is a strong and highly specific inhibitor of sodium-glucose cotransporter 2 with notable antihyperglycemic effects. By inhibiting SGLT2, dapagliflozin decreases glucose reabsorption in the kidneys and promotes glucose excretion while maintaining glycemic control. [5, 6]

Analytical quantification for dapagliflozin as well as linagliptin has been obtained from previous studies using a variety of methods, including separate analyses and co-analysis with additional pharmacological components.[7-9] The simultaneous measurement for dapagliflozin as well as linagliptin in a single pharmaceutical dosage form using reverse-phase high-performance liquid chromatography (RP-HPLC), on the other hand, is still an unresolved aspect of the body of existing work. In order to simultaneously measure these drugs in tablet formulations, a QbD-required RP-HPLC technique was created and validated.

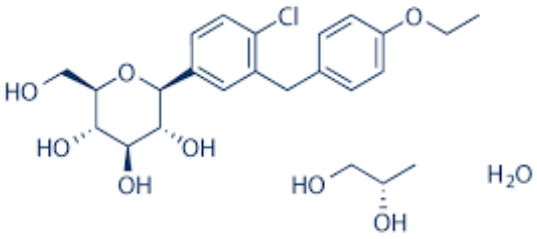


Fig 1- Dapagliflozin Propandio

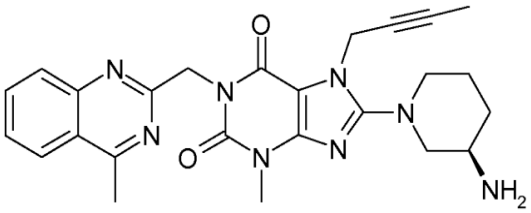


Fig 2- Linagliptin's Structure

Monohydrate's Structure

MATERIAL AND METHODS:

Chemicals:

Dapagliflozin were acquired from Alkem Laboratories,Navi Mumbai, India. and Linagliptin were acquired from Umedica Laboratories,Navi Mumbai, India. Reagents like ACN & MeOH (HPLC grade) were secured from Mumbai, India's Merck Life Science Pvt. Ltd. Ortho-phosphoric acid (OPA) were received from Thermosil Fine Chem Industries in Pune, India. Tri ethyl amine was provided by Loba Chemicals Pvt. Ltd. Mumbai. HPLC (Milli-Q) Water were In-house supply.

Equipment and Chromatographic Parameters:

The chromatographic assessment was conducted utilizing a HPLC system, specifically the JASCO PU 2075 Plus, which was operated using Borwin software. The separation took place on a column Qualisil 5 BDS C8 measuring 250 × 4.6 mm and particle size of 5 µm. A binary mobile phase comprising a 50:50% (v/v) Combination of acetonitrile and a 0.1% ortho-phosphoric acid solution, which was brought to a pH of 3.5 by adding triethylamine, was used to optimize the chromatographic variables. A 1 mL/min flow rate, a 230 nm detector wavelength, and a 20 µL injection volume were all used in the analysis procedure. In order to guarantee sufficient separation and quantification, the analytical time period was conceptually limited to 8 minutes.

Preparations of Stock Solutions and Mobile Phase:

0.1% Ortho Phosphoric Acid (OPA) Solution Preparation :

A 0.1% w/w ortho-phosphoric acid solution was prepared by quantitatively transferring 0.1 milliliters of the ortho-phosphoric acid solution to a 100 milliliter volumetric flask that was filled with HPLC-grade ultrapure water. A diluted solution of triethylamine was then used to bring the pH of this solution down to 3.5. To guarantee purity and remove particle impurities, the buffer solution was lastly filtration-sterilized using a membrane filter with a

nominal pore size of 0.45 microns.

Mobile Phase Preparation:
Acetonitrile of high-performance liquid chromatography (HPLC) grade was subjected to ultrasonic assisted degassing for a period of 30 minutes to minimise dissolved gas content. Meanwhile, the pH of an ortho-phosphoric acid buffer solution was accurately adjusted to a value of 3.5 through the application of triethylamine in diluted form, subsequent to which, the solution was subjected to 30 minutes of ultrasonic degassing. Ultimately, a mobile phase was formulated comprising a 50:50 volumetric ratio of ortho-phosphoric acid buffer (expressed as 0.1% by volume) and HPLC grade acetonitrile.

Preparation of Diluent:
A binary solvent mixture composed of equal proportions of acetonitrile (ACN) and water (50:50V/V) was employed as the diluent throughout the study.

Preparation of Standard Solution:
A precise quantity of 10 mg of Dapagliflozin Propanediol Monohydrate (DPM) and 5 mg of Linagliptin were accurately measured and placed in distinct 100 ml volumetric flasks. Initially, 10 mL of solvent, comprising deionized water for DPM and acetonitrile for Linagliptin, were added to each flask. Subsequent sonication for 10 minutes facilitated dissolution.Following sonication, 20 mL of a diluent were introduced, and the mixture underwent additional sonication and periodic agitation for 30 minutes. The resultant solution was then brought to 100 mL in volume utilizing the diluent.

The prepared solution was filtered utilizing a 0.45 µm membrane filter to yield Stock Solution A. 1 mL of DPM and 0.5 mL of Linagliptin from the initial stock were subsequently isolated for further analysis.

Mixed Standard Solution Preparation:
A precise 1 mL sample was taken from each primary stock solution of DPM and Linagliptin, and carefully transferred in a 10 milliliters volumetric flask. The resulting volume then adjusted to the calibration mark with the specified diluent. This process resulted in a final mixed standard solution with Dapagliflozin Propanediol Monohydrate with a concentration of 10 µg/mL and Linagliptin at 5 µg/mL.

Sample Solution Preparation:
A total of 20 tablets was subjected to collective weighing and served as a basis for establishing the mean weight. Subsequently, the tablets underwent meticulous pulverization in order to ensure uniformity. A predetermined quantity of 0.204 g was accurately measured, translating to 10 mg of Dapagliflozin Propanediol Monohydrate and 5 mg of Linagliptin, which was then introduced into a 100 mL volumetric flask. To enhance dissolution, a specified volume of solvent was added; 20 mL of water was incorporated for Dapagliflozin Propanediol Monohydrate, whereas 15 mL of acetonitrile was utilised for Linagliptin. A further addition of 20 mL of diluent facilitated the calibration of the resultant solution to 100 mL, following a 10-minute sonication process to promote solubility. The resultant mixture underwent filtration to eliminate any undissolved particulate matter. Thereafter, the resultant working standard solution, which comprised 100 µg/mL of Dapagliflozin Propanediol Monohydrate and 50 µg/mL of Linagliptin, was further diluted as required to achieve the requisite concentrations for subsequent analytical evaluation.

Determination of Working Wavelength (λmax):
The individual and overlay spectrum were recorded for Linagliptin and DPM the range of 200-400nm. The maximum Absorption for Linagliptin and DPM were found to be 224nm and 245nm. The isoabsorptive point was found to be 215nm. Though the isoabsorptive point was 215nm, both the drugs showed good absorbance at 230nm. Hence for the present study 230 nm is used as wavelength of determination.

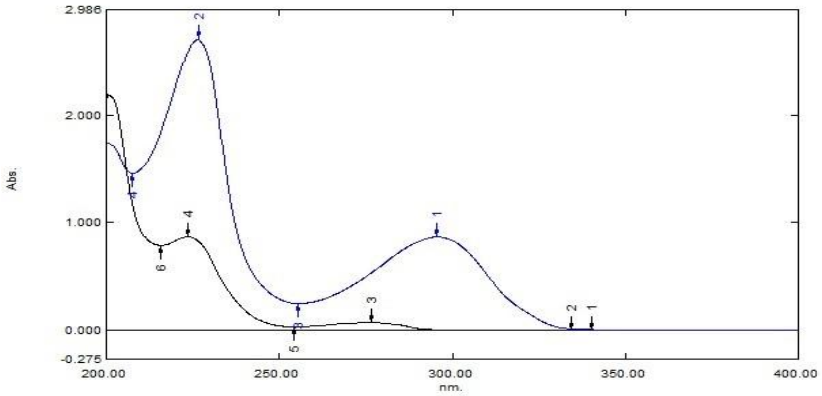


Fig.3: UV Spectrum Overlay of Dapagliflozin Propanediol Monohydrate and Linagliptin.

Assay of marketed formulation:
Chemical analysis was conducted via repeated injections of the sample solution into a high-performance liquid chromatography (HPLC) system, using a solution comprising 30µg/ml of DPM and 15µg/ml of LINA. Peak areas were quantified and employed to calculate assay percentage and relative standard deviation (%RSD).

Early Method Development and Validation by Using the QbD Approach:
The Quality by Design (QbD) framework, in combination with **DoE**, was implemented to establish a robust analytical procedure. The method development process was divided into two primary phases:[10]
1. Screening Phase (SP)
2. Final Optimization and Statistical Analysis (SAFO)

Phase of Screening: The initial phase involved employing DoE (version 13.0.5.0) to systematically assess key variables such as wavelength, flow rate, and acetonitrile (ACN) ratio, aiming to optimize method performance. Table 1 provides the levels of these parameters. To evaluate their impact, resolution and theoretical plates were chosen as response variables, given their significance in determining overall method efficiency. Initially, a 3^3 factorial design was applied, incorporating three factors at three levels. However, upon recognizing non-linearity in the response, the study proceeded with a Box-Behnken design for refined optimization. The experimental plan and results derived from DoE are mention in Table 2.

Statistical Analysis and Final Optimization:
The outcomes from the experimental trials were input back into Design Expert software, where 3D response surface plots and graphical plots is generated. These visualizations illustrated the influence of critical parameters on key quality attributes. By analyzing these plots, it was possible to identify which method parameters yielded the most favorable results. Based on these insights, the final optimized chromatographic conditions were determined. Additionally, statistical tools such as ANOVA (Analysis of Variance) were employed for individual response evaluations. The p-value was used to assess the statistical significance of each selected parameter in the study, ensuring a well-validated method development approach.

Validation of Optimized Method:
Analytical Validation procedures was performed by using the following parameters for LINA And DPM

1. System suitability
The system suitability was evaluated by injecting six replicates of 30µg/ml of DPM and 15µg/ml of LINA The parameters like (NTP) theoretical plates, resolution, peak area, tR and tailing factor were estimated. The %RSD of this parameters
are within the limit. i.e. (<2)

Table 1: Factore and Levels of Independent Variables

C M Ps	Unit	Type	Sub-type	Minimum	Maximum
Wavelength	NM	Numeric	Continue	228	232
Flow-Rate	mL/Min	Numeric	Continue	0.8	1.20
ACN	%	Numeric	Continue	40	60

Table 2: Box –Behnken Design Plan and Responses

		Component1	Component 2	Component3	Outcome 1	Outcome 2	Outcome 3
Std	Run	Wavelength (NM)	Flow Rate (ml/min)	ACN Ratio	NTP of DPM	NTP of Linagliptin	Resolution
16	1	230	1	50	3896	3284	8.42
1	2	228	0.8	50	2867	1922	5.02
10	3	230	1.2	40	1840	1507	8.17
9	4	230	0.8	40	2866	1844	4.91
6	5	232	1	40	2174	1888	9.67
14	6	230	1	50	3890	3280	8.4
2	7	232	0.8	50	1711	866	5.1
15	8	230	1	50	3799	3282	8.41
4	9	232	1.2	50	2671	1899	9.55
13	10	230	1	50	3696	3280	8.42
11	11	230	0.8	60	1480	1824	4.91
12	12	230	1.2	60	2070	2255	6.49
17	13	230	1	50	3890	3284	8.42
8	14	232	1	60	1726	1737	4.51
7	15	228	1	60	1728	1799	4.63
5	16	228	1	40	2158	1822	9.6
3	17	228	1.2	50	2653	1779	9.42

2. Linearity:

To assess linearity, mixed standard solutions of multiple concentrations (three replicates each) were assessed within specified ranges for the analytes Linagliptin and Dapagliflozin Propanediol Monohydrate (10-50 µg/ml and 5-25 µg/ml, respectively). Linear relationships were observed for both compounds within the designated concentration ranges. A calibration curve was generated by plotting peak area against the corresponding analyte concentration and a correlation coefficient was subsequently calculated to confirm the linearity of therelationships.

3. Accuracy:

Accuracy was assessed by injecting the solutions in triplicates at 80%, 100% and 120% level. Spiking the preanalysed sample with standard drug and mixture solutions were reanalysed. calculated the amount found and % recovery.

4. Precision:

4.1 System Precision:

Duplicate injections of six mixed standar solutions were performed, comprising concentrations of 30µg/ml DPM and 15µg/ml LINA, onto an HPLC system to assess system precision.Peak areas were quantified and relative standard deviation (% RSD) values were subsequently calculated.

4.2 Method Precision:

The six replicate of sample solution containing 30µg/ml of DPM and 15µg/ml of LINA have been analysed for method precision. The % assay and % RSD was calculated.

4.3 Intermediate Precision

1. Intraday precision and Interday precision

Three distinct analyte concentrations, composed of 20, 30, and 40 micrograms per milliliter of DPM and 10, 15, and 20 micrograms per milliliter of LINA, were administered to the high- performance liquid chromatography (HPLC) system at varying time intervals on the same and different days to assess intraday and interday variability, with relative standard deviation (%RSD) calculated as a measure of precision.

5. Specificity:

Specificity was performed by comparing blank, sample and standard solution 30µg/ml of DPM and 15µg/ml of LINA into HPLC system. Chromatograms were reported.

6. Robustness:

Two parameters from the optimal chromatographic condition were changed to test the method's resilience.The content of the mobile phase varied by ±2, and the flow rate varied by ±02 ml. Determine the percentage RSD.

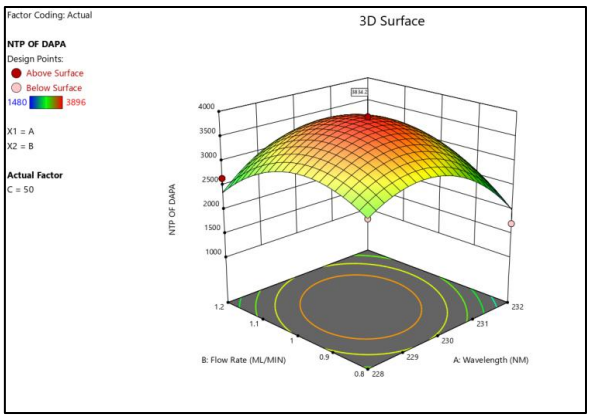
7. Ruggedness:

Ruggedness was assessed by analysts 1 and 2 on the same day after sample solutions containing 30 µg/ml of DPM and 15 µg/ml of LINA were injected into the HPLC apparatus. computed the RSD percentage.

8. Limit of Detection (LOD) and Limit of Quantitation (LOQ):
By injecting the lowest concentration of a standard solution at which the peak was found, LOD and LOQ were established.
LOD= 3.3σ/slope
LOD= 10σ/slope

RESULT AND DISCUSSION:

Statistical Analysis of Experimental Data:
(SAOED) Using Design -Expert (DOE)Software:
As shown in Table 2, the statistical significance of the generated model with respect to the Three response variables was assessed using the (ANOVA) Analysis of Variance. Design Expert® software was used to analyze the 2D contour and 3D surface plots in order to determine how various parameters and their interactions affected the response. Different response levels are shown by the color gradient in these graphs, where greater values are indicated by dark red and lower values by dark blue. Light blue, green, and yellow hues are used to represent intermediate values.[11]



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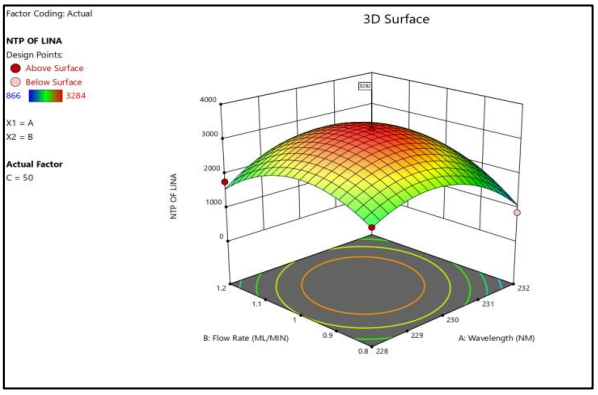

(b)

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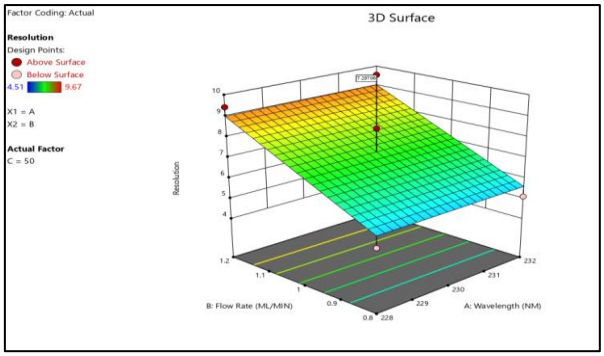

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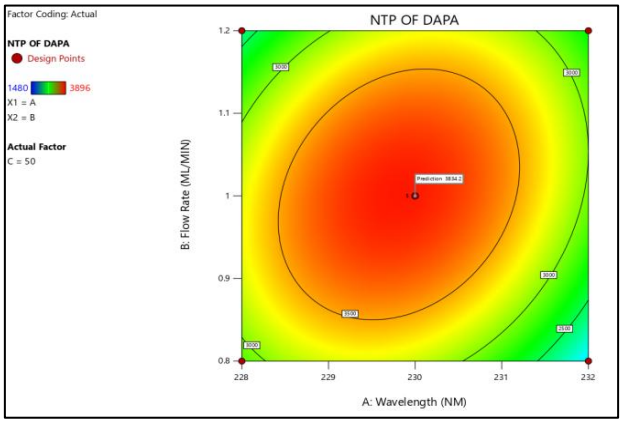

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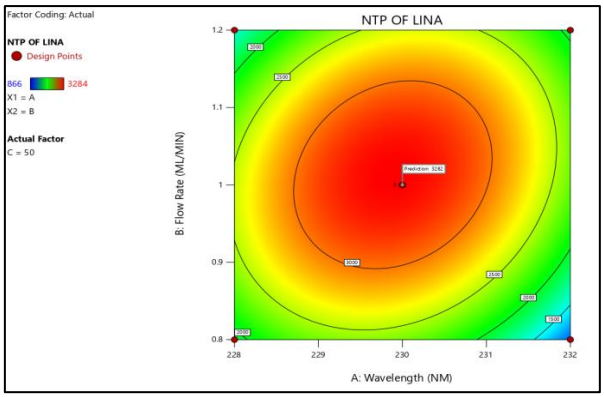

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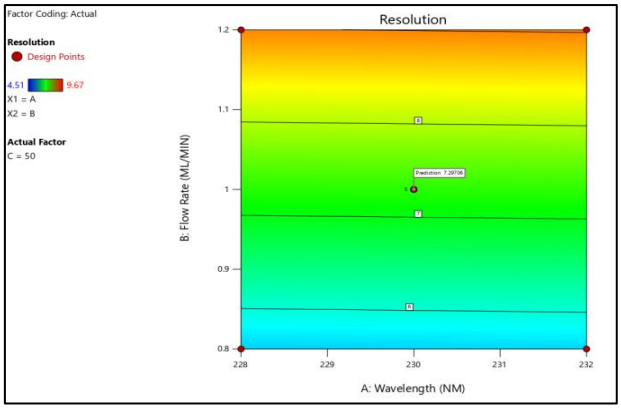

(c)

Fig. 4: 3d Surface Plot Of Ntp Of Dpm (A), Ntp Of Linagliptin (B), Resolution Between Dpm And Lina (C), 2d Contour Of Ntp Of Dpm (A), Of Linagliptin (B), Resolution Between Dpm And Lina (C).

The 2D contour plots and 3D surface plots (Fig. 4) illustrate the relationship between wavelength, flow rate, and acetonitrile (ACN) ratio in the context of **NTP** (Number of Theoretical Plates) for Dapagliflozin Propanediol Monohydrate (DPM) and Linagliptin (LINA), as well as Resolution. The color coding in these plots allows for easy identification of the working region:

- Warm red shades represent higher NTP values for DPM.
- Cold blue shades indicate lower NTP values for DPM.
- Intermediate values range from light green to yellow.

Optimization Using the Desirability Function:

Following the software's processing of all experimental data, a 3D response surface was produced. A composite desirability function that established goals and limits for every response was used to identify the ideal circumstances. From d = 0 (unwanted outcome) to d = 1 (ideal outcome), the desirability Function on a scale The ideal flow rate determined to be 1.0 mL/min by establishing target objectives and restrictions for theoretical plates (NTP), resolution, and composite desirability (D) = 1, as shown in Figure 6.

Three triplicate injections containing 10µg/mL of Dapagliflozin Propanediol Monohydrate (DPM) and 5µg/mL of Linagliptin were examined in order to validate these ideal conditions. The findings showed that the theoretical plates and observed resolution nearly matched the expected values. The accuracy of the optimization was confirmed by the observed discrepancies between the actual and anticipated peak responses, which were less than 5%. Figure 6 displays the final optimized chromatogram.[12]

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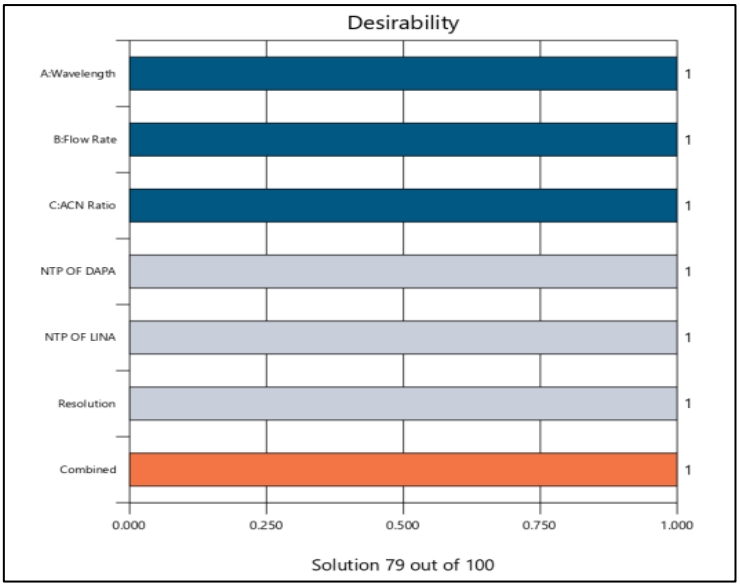

Fig.5: Overall Desirability of Final Method

Table 3: Final Optimized Hplc Chromato-Graphic Conditions

Property	Mobile Phase	Wavelength	Flow Rate
Value	0.1%OPA: Acetonitrile (50:50%V/V)	230 NM	1ML/MIN

The chromatographic parameters (pH and mobile phase composition) were refined over a number of trials to yield better peak shape and increased sensitivity for both medications. Numerous combination ratio experiments were carried out. For the last chromatographic separation, a Qualisil 5 BDS column C8 (250 x 4.6 mm 5 um particle size) was employed. ACN: 0.1%OPA buffer (50:50%v/v) pH-3.5 adjusted with TEA at a volume flow rate of 1.0 mL/min with a 20 µl injection volume; a PDA detector operating for 8 minutes detected the wavelength at 230 nm. Linagliptin and DPM were found at tR of 2.675 and 4.943 minutes, respectively, under the chromatographic conditions previously mentioned. The optimized process was validated in accordance with ICH guidelines. Dapagliflozin with linagliptin's typical chromatogram is displayed in the fig 6.

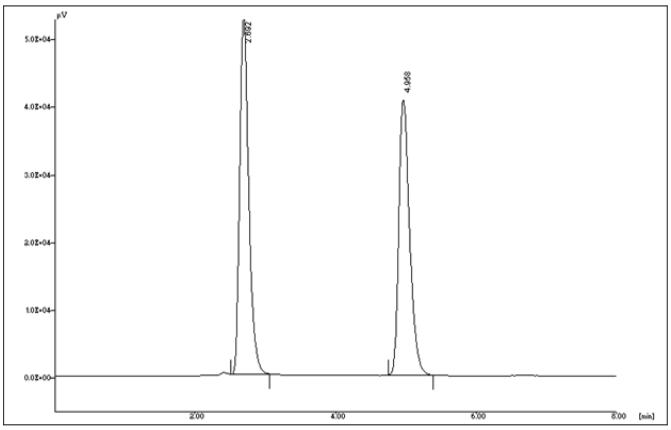

Fig 6- Typical chromatogram of DPM & LINA

System suitability

System suitability data for both LINA and DPM are presented in Table 4, revealing that all assay parameters fall within the predetermined acceptance threshold, thus validating the method's efficacy for quantitative analysis of the aforementioned compounds.

Table 4: Parameters of System suitability data of DPM and LINA

Parameters	Dapagliflozin Propanediol Monohydrate	Linagliptin

Sr. No.	tR	T F	NTP	Peak Area	Resolution	tR	TF	NTP	Peak Area
1	4.95	1.37	5715	1295959	9.62	2.68	1.33	2602	1243143
2	4.94	1.34	5615	1295850	9.62	2.67	1.32	2604	1241410
3	4.95	1.34	5715	1295959	9.62	2.68	1.3	2612	1243143
4	4.95	1.36	5715.2	1291954	9.63	2.66	1.33	2602	1241143
5	4.95	1.32	5615.7	1294959	9.6	2.68	1.33	2602	1239143
6	4.92	1.37	5715	1295954	9.6	2.68	1.31	2626	1242143
Mean	4.943	1.341	5681.817	1295105.833	9.615	2.675	1.32	2608	1241688
(±) SD	0.011	0.0186	46.99952	1453.992	0.011	0.0076	0.0115	8.793937	1371.885
%RSD	**0.223**	**1.39**	**0.827**	**0.112**	**0.116**	**0.285**	**0.874**	**0.337**	**0.110**

Linearity:

The linearity plot depicts a linear relationship between DPM and LINA calibration standards within specified concentration ranges of 10-50µg/ml and 5-25µg/ml, respectively. Both analytes exhibit high degrees of correlation, with associated correlation coefficients of 0.9991 and 0.9994 for DPM and LINA, respectively.

Table 5: Linearity data of LINA and DPM

Parameters	LINA	DPM
Linearity Values	5-25µg/ml	10-50µg/ml
Regression equation	Y =77548x + 53673	Y=42326x - 1878
Slope	77548	42326
Y- Intercept	53673	1878
r^2	0.9994	0.9991

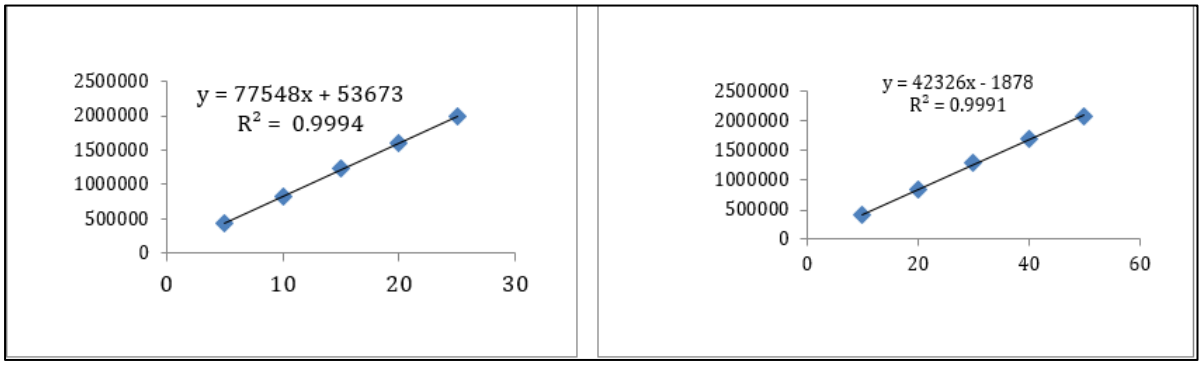

Fig7- Linearity plot for DPM and LINA

Precision:

The precision of LINA and DPM was evaluated based on the coefficient of variation, and results revealed all precision levels fell within acceptable ranges as mention in table 6.

Table 6: Precision of DPM and LINA

Parameter	Precision of Method	Precision of System	Precision of Intraday	Precision of Interday
LINA (%RSD)	**0.117**	**0.101**	**0.103**	**0.239**
DPM (%RSD)	**0.106**	**0.114**	**0.578**	**0.564**

Specificity

Comparing the blank chromatograms (fig. 8), working standard (30µg/ml and 15 µg/ml) (fig. 9), and sample solution (30µg/ml and 15 µg/ml) (fig. 10) in triplicate allowed for the determination of the method's specificity. The procedure was specific because there was no any error from the excipients and components of the mobile phase during the standard and sample retention times.

Fig.8: Blank chromatogram

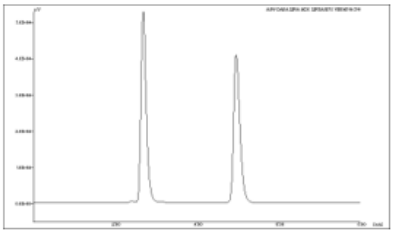

Fig.9: Std chromatogram

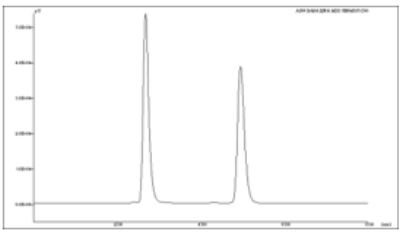

Fig.10: Sample chromatogram

Accuracy:
By spiking the sample into a reference solution at three different levels 80%, 100%, and 120% the accuracy was ascertained. The recovery percentage for DAPA and LINA was found to be well within the acceptable ranges, ranging from 99.98 to 100.01% at all levels. The accuracy of the procedure for calculating DAPA and LINA is confirmed by percentage recovery. The recovery study percentages displayed in Tables 7 and 8.

Assay:
Assay of marketed formulation for DPM and LINA were found to be 99.916% and 99.9% respectively. The result of assay shown in Table 9.

Robustness:
By changing two parameters from the ideal chromatographic setting, robustness was remained. The flow rate varied by ±0.2ml and mobile phase composition varies by ±2. The result of robustness is given Table-10.

Ruggedness:
Ruggedness was determined by injecting sample solutions of 30µg/mL DPM & 15µg/mL LINA into HPLC system and evaluated by analyst 1 & analyst 2 on a same day. %RSD of both drugs are within acceptance limit. The result of ruggedness is given in Table-11.

Table 7: % Recovery values of DPM

Level of Recovery	Amt of drug from sample (µg/ml)	Amt. of standard added (API) (µg/ml)	Area of spiked sample (A)	Area of unspiked sample (B)	Area of Std (C)	Amt recovered (µg/ml)	% Recovery	Avg	SD	% RSD
80%	15	9	1046990	645651	401302	24.02	100.12	99.956	0.116	**0.116**
			1046845	645651	401302	23.97	99.89			
			1046598	645650	401312	23.96	99.86			
100%	15	15	1294102	645651	648349	29.96	99.89	99.923	0.108	**0.108**
			1294302	645650	648390	30.02	100.07			
			1294652	645651	648349	29.94	99.81			
120%	15	21	1511462	645651	865912	35.96	99.89	99.95	0.106	**0.106**
			1511521	645650	865901	36.03	100.1			
			1511532	645651	865914	35.94	99.86			

Table 8: % Recovery values of Lina

Level of Recovery	Amt. of drug from sample (µg/ml)	Amt. of standard added (API) (µg/ml)	Area of spiked sample (A)	Area of unspiked sample (B)	Area of Std (C)	Amt recovered (µg/ml)	% Recovery	Avg	SD	% RSD
80%	7.5	4.5	1022651	623512	398930	12	100.02	100	0.016	**0.016**
			1022457	623510	398931	12	100			
			1022567	623512	398930	11.99	99.98			
100%	7.5	7.5	1242723	623512	619321	15	100	99.98	0.012	**0.012**
			1242633	623510	619321	14.99	99.98			
			1242542	623512	619320	14.99	99.97			
120%	7.5	10.5	1465620	623512	841830	17.81	98.99	99.66	0.473	**0.473**
			1465659	623512	841832	17.99	99.99			
			1465512	623510	841830	18	100			

Table 9: Assay of DPM and LINA

Drugs	Avg. Sample Area	Avg.Std Area	Mean % Assay
Dapagliflozin Propanediol Monohydrate	1294726	1295265	**99.91%**
Linagliptin	1241976	1242591	**99.90%**

Robustness Parameters		Dapagliflozin Propanediol Monohydrate			Linagliptin		
		tR	**T F**	**Peak Area**	**tR**	**T F**	**Peak Area**
Flow Rate (ml/min)	0.8 ml	5.211	1.27	1294856	2.45	1.33	1242140
		5.332	1.27	1294958	2.42	1.32	1242154
		5.221	1.27	1291956	2.20	1.30	1240145
	1.0 ml	4.912	1.37	1295959	2.68	1.33	1243143
		4.923	1.34	1295850	2.67	1.32	1241410
		4.921	1.34	1295959	2.68	1.30	1243143
	1.2 ml	4.613	1.34	1296956	2.80	1.23	1243952
		4.721	1.35	1292956	2.80	1.32	1241852
		4.732	1.35	1295856	2.70	1.34	1244954
Mean		4.954	1.322222	1295145	2.60	1.34	1242543
(±) SD		0.250971	0.037941	1629.908	0.189326	0.030912	1347.5699
%RSD		**0.250**	**0.342**	**0.125**	**0.180**	**0.300**	**0.108**

Table 10: Robustness of DPM and LINA

Robustness Parameters		Dapagliflozin Propanediol Monohydrate			Linagliptin		
		tR	**T F**	**Peak Area**	**tR**	**T F**	**Peak Area**
Mobile Phase Composition	52:48	4.875	1.33	1297959	2.677	1.30	1253143
		4.898	1.34	1296850	2.674	1.32	1247410
		4.796	1.32	1295959	2.680	1.30	1253143
	50:50	4.912	1.37	1295959	2.681	1.33	1243143
		4.923	1.34	1295850	2.672	1.32	1241410
		4.921	1.34	1295959	2.680	1.30	1243143
	48:52	4.910	1.30	1297959	2.676	1.31	1253113
		4.825	1.31	1296850	2.673	1.34	1257410
		4.891	1.34	1298959	2.684	1.32	1253123
Mean		4.883444	1.332222	1296923	2.677444	1.315556	1249449
(±) SD		0.042029	0.019309	1066.758	0.003833	0.013426	5435.544
%RSD		**0.860**	**1.449**	**1.449**	**0.143**	**1.02**	**0.435**

Table 11: Ruggedness of DPM and LINA

Drug	Analyst 1 Average peak area	(±) SD	%RSD	Analyst 2 Average Peak area	(±)SD	%RSD
DPM	1295106	1453.993	0.112	1294939	1817.579	**0.140**
LINAGLIPTIN	1241688	1371.885	0.110	1241021	2738.057	**0.220**

LOD and LOQ:

The LOD and LOQ were reported to be 1.0063 and 3.0496 µg/ml for DPM and for LINA0.7241 and 2.1944 µg/ml respectively.

CONCLUSION:

Linagliptin and Dapagliflozin Propanediol Monohydrate can be measured simultaneously in tablet formulations using an RP-HPLC method that was successfully designed and validated with the help of Quality by Design. The validation methodology verified that the method satisfies all analytical performance criteria and is extremely sensitive, precise, accurate, robust, rugged, and selective. Linagliptin and Dapagliflozin Propanediol Monohydrate in pharmaceutical dosage forms can thus be routinely analyzed for quality control using this enhanced approach.

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