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Quantitative computation and stability evaluation of phase III composition comprising sitagliptin and dapagliflozin propanediol monohydrate by RP-HPLC

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ABSTRACT

It is always quite essential to evaluate stability performance of any formulation before it enters into the commercial market or available for the clinical trial and so is the case with formulation containing sitagliptin and dapagliflozin propanediol monohydrate, which is at present in clinical phase-III trial. With the same perspective, a reverse phase high performance liquid chromatography was engineered for quantification of both components in presence of their degradation products formed during stress testing. Elution was achieved on Inertsil ODS C_{18} column with Methyl Nitrile (25 parts) and 0.02 M KH_2PO_4 buffer 0.02 M having 1 ml triethylamine with neutral pH adjusted by orthophosphoric acid (75 parts) in isocratic mode (flow rate of 1 ml/minute), while chromatogram was monitored at 210 nm. All system suitability parameters are indicative of excellent separation. Analysis of stressed samples (according to ICH Q1) showed that the household formulation showed oxidative instability and overall results of forced stress were predictive in nature. The optimized analytical technique was subjected to validation (according to ICHQ1 guideline) and was observed to be highly reproducible with greater level of specificity, and therefore can be practiced for routine quantification of sitagliptin and dapagliflozin propanediol monohydrate from proposed formulation.

INTRODUCTION

When we discuss about sitagliptin (SITA), it is chemically a trizole derivative with pyrazin moeity which exerts its physiological action which is priliminary hypogyclemic action thorugh inhibition of dipeptidyl peptidase-4 system. This active chemical substance is used in combination with diet and exercise in type-2 diabetes either alone or combination with other oral hypoglycemic agents for having potential antidiabetic action (Zerilli and Pyon, 2007). On contrast, dapagliflozin propanediol mnohydrate (DAPA), is chemically an oxane deriavtive with triol moeity and having hypoglycemic action through supression of sodium-glucose cotransporter-2 system, which is again available in combination of other oral hydpogycemic agents oprating on different priciple for better gycemic control (Dhillon, 2019).

Extensive literature search on SITA highlights majorly UV spectroscopy (Pathade *et al*., 2011; Pritam *et al*., 2011), high performance liquid chromatography (HPLC) (Patel *et al*., 2014; Peraman *et al*., 2013; Ramalingam *et al*., 2014; Suneetha *et al*., 2020), LC-MS (Burugula *et al*., 2013; Reddy *et al*., 2015), and HPTLC (Manasa *et al*., 2015; Modi *et al*., 2013) as analytical methods for analysis from bulk and pharmaceutical dosage form. In similar way, detailed literature review revealed UV (Jani *et al*., 2015; Mante *et al*., 2017), HPLC (Deepan *et al*., 2017, 2018; Sanagapati *et al*., 2014; Usman *et al*., 2020), LC-MS (Aubry *et al*., 2010; El-Zaher *et al*., 2019), and HPTLC (Abdelrahman *et al*., 2020; Suma *et al*., 2019) method for determination of DAPA in bulk and pharmaceutical dosage form.

At present, several clinical trails and literature are sugegstive of better management of glycemic control in type-II diabetes with reduction in glycated haemoglobin when SITA

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and DAPA are administerd in a combination at a does level of 10 mg of DAPA and 100 mg of SITA (Jabbour *et al*., 2014; Medical Professionals reference, 2012). The literature survey revealed only one reverse phase high performance liquid chromatography (RP-HPLC) method for quantification of both the components which has serious limitation. Based on above-mentioned facts, it was decided to develop and validate a new, simple, precise and accurate, stability indicating RP-HPLC method for the determination of DAPA and SITA in synthetic mixture.

MATERIALS AND METHODS

Instruments and chemicals

AGILENT (Series 1260 infinity) HPLC unit equipped with autosampler having provision of UV-VIS detector and capable of quaternary gradient operation was used to process the samples, while OPENLAB sofftware was used to process and integrate the obtained chromatogram. The columns employed were INERTSIL ODS C_{18} and HIBAR ODS C_{18} having dimensions of 250 mm as length and 4.6 mm internal diameter. Mettler Toledo weighing balance was used to weigh accurate quantities of samples having sensitivity of 0.1 mg.

Both active components were received as gift samples from Cadila Healthcare Limited, Gujarat (Batch No: SA0010119 for SITA and GLI500119 for DAPA) while other solvents like Methyl alchohol, methyl nitrile, KH_2PO_4 buffer and water were of HPLC grade and procured from Merck life scieces private limited, Mumbai.

Optimization of separation conditions

Discrite intrinsic physico-chemical parameters of active components were studied but atmost priority was given to solubility and pKa value. Other instrumental parameters like flow rate and temperate were also studied to check effect on retention time of eluting components. Owning to the vast difference in polarity of components, ODS C_{18} column was fixed as stationary phase which encourages the retention of nonpolar and early elution of polar component. To get adequate separation in conjuction with system suitability parameters, various elution systems were studied.

Chromatographic conditions

Adequate separation was achived by utilizing methyl nitrile as organic phase in 25 parts and 75 parts of 0.02 M potassium dihydrogen phosphate buffer containing 1 ml triethylamine (TEA) having neutral pH adjusted by orthophosphoric acid (10%) as aqueous phase. The mixed elution system was screened through 0.45 µ membrane filter and was also utilized as dilution medium for components. The above-methioned elution system was allowed flow though INERTSIL ODS C18 column in isocratic mode at flow rate of 1 ml/minute with monitoring on 210 nm as wavelength where both components gave significant signal. Futhermore, suitability of this system was also assesed by system suitability parameters for which total five injections of fixed concentration was injected at 20 µl injector volume.

Forced degradation conditions

Acid and base hydrolysis

To check the stability with respect to hydrolysis by acidic condition, 5 mg of DAPA and 50 mg of SITA was tretaed with 5 ml of 0.1 N HCl and 4 ml of elution medium, the resulting mixture was refluxed at 60°C for half and hour which was followed by cooling of content and neutralization with 0.1 N NaOH. 0.2 ml of previous solution was further diluted to 10 ml with elution medium (Treated sample). In contrast, for base hydrolysis, 0.1 N NaOH was used as the treatment medium and 0.1 N HCl was used as the neutralizing medium. All other condition were same as that of acid hydrolysis. To compare the results, 0 hour sample and blank was prepared. 20 µl of 0 hour sample and treated sample was injected on to column and comparison was made to determined % degradation.

Oxidative hydrolysis

Effect of oxidative stress was imparted to both drug by use of 3% hydrogen peroxide. Here in this case, 5 mg of DAPA and 50 mg of SITA was tretaed with 5 ml of 3% H_2O_2 and 4 ml of elution medium, the resulting mixture was refluxed at 60°C for half and hour which was followed by cooling and again volume was adjusted upto the mark. 0.2 ml of the above solution was further diluted to 10 ml with elution medium (treated sample). In similar way, 0 hour sample and blank solution was prepared and were injected on to column to assess the % degrdation achieved.

Thermal hydrolysis

To asses impact of dry heat on the stability of DAPA and SITA, both componets in preweight quatity (10 and 100 mg, respectively) were exposed to dry heat in a hot air oven at 80°C for about half hour. Treated contents were diluted upto 10 ml with mobile phase and 0.1 ml of same solution was further raised to 10 ml which was injected at 20 µl volume on to column to assess % degradation.

Validation of optimized method

All validation parameters are studies as per ICH Q2R1 guidelines, execution procedure of each is discussed below.

Linearity and range

To study linearity and range, accurately weighed quantities of 5 mg DAPA and 50 mg SITA was diluted to 10 ml with elution medium to produce stock solution containing 500 µg/ml DAPA and 5,000 µg/ml of SITA. Various aliquotes were transferred to 10 ml volumetric flask and volume of each raised to 10 ml to give mixtures having concentration of 5 + 50 µg/ml to 15 + 150 µg/ml of DAPA and SITA, respectively. Each concentration was injected at 20 µl injector volume and response obtained was plotted against concentration to observe linear regression coefficient.

Repeatability

For adjudging repeatability of method, each concentration form range was injected for five times and each level is observed for relative standard deviation (RSD).

Limit of detection and quantitation (LOD/LOQ)

Detection limit as well as qunatification limit was calculated statistically by utlization of regression data from repeatability. Standard devidation of standard error (σ) and average of slope (S) were used to process LOD and LOQ.

Accuracy

As it refers to the % recovery of analyte in presence of exipients, it was practiced by spiking of placebo with standard at 50%, 100%, and 150% of target concentration. Each concentration was injected for three times and % recovery was calculated on the basis of onserved area at each spiking level (by utilization of linear regression analysis).

Method precision

This parameter was studies by injecting individual concentration that represents overall range are studies on same day and between days and for the same mixture of DAPA and SITA that represents overall range (8 + 2, 16 + 4, and 24 + 6 µg/ml) were analyzed on the same day at different time interval for intraday precision and different day for interday precision. Each oncentration was analyzed for three times and was monitored for RSD at each level.

Robustness

To study the effect of minor variations of method parameters on to the results, operation parameters like temperature, pH of mobile phase and flow rate was delibrately altered within acceptable range and effect of the same was observed on the system suitability parameters as retention time and % assay, which was also monitored for relative standard devidation.

Ruggedness

This parameters refers to the method repeatability and was studied by utilizing the diffent column having same specification and to be more precise HIBAR ODS C_{18} column was employed and difference in the area obtained from both was monitored through student *t*-test.

Assay of synthetic mixture

Weight accurately 10 mg of DAPA, 100 mg of SITA with placebo in 10 ml calibrated volumetric flask. Contents diluted up to 10 ml calibrated volumetric flask with methyl alcohol and filter the solution. 1 ml of master stock solution further dilute up to 10 ml with mobile phase. 1 ml filtrate diluted up to 10 ml with mobile phase (10 + 100 µg/ml). Resulting solution was chromatographed in triplicates and mean observed area was statistically transformed by linear regression equation to get toal % of DATA and SITA in synthetic mixture.

RESULTS AND DISCUSSION

Optimized chromatographic conditions

Initially trials were initiated using combination of methyl nitrile and water in equal proportion but distroted peak without any sort of separation were observed. As separation was not observed in the previous case, methyl alcohol was introduced in to the system but with the same only DAPA was detectd. In all the cases, flow rate was 1.2 ml/minute. All the results were monitored at wavelengths as 210, 224, and 267 nm. Due to previous observed problems, 0.02 M KH_2PO4 (0.02 M) containing 1 ml TEA and pH adjusting to 7 by orthophosphoric acid in equal volumes was used as elution medium. Here, both the peak were detected but still were eluting closely to each other. So in the next trial the proportion of buffer was increased and flow rate was further reduced to 1 ml/minute. Even the solution of DAPA and SITA were also prepared in the mobile phase. When method was operated using later discussed chromatographic conditions, well resolved peak of DAPA and SITA was observed at 2.89 and 16.41 minutes, respectively (Fig. 1). The detection wavelength was kept at 210 nm as linearity and peak shape for both the components were perfact at this wavelength. All the system suitability paramerets were within United States Pharmacopoeia guidelines with RSD of less than 1. All the system suitability paramerets have been highlighted in Table 1. The newly developed method was found to be superior to reported method (Gupta and Mishra, 2021) by far degree as they had employed gradient elution with potassium phosphate monobasic buffer pH (3.0) as mobile phase A while methanol and acetonitrile in the ratio of (60:40 v/v) as a mobile

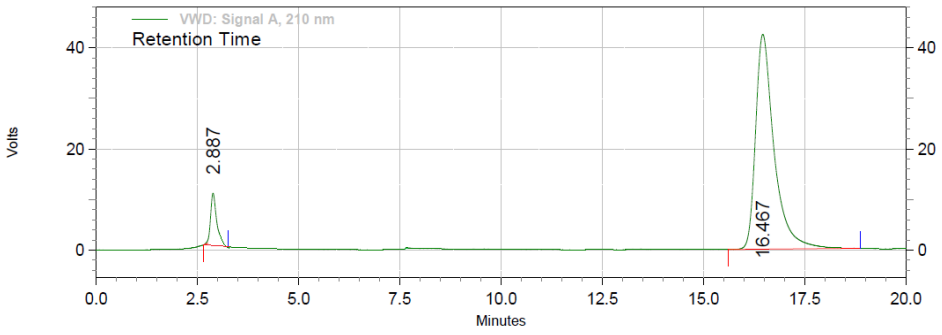

Figure 1. Chromatogram of mixture of DAPA and SITA under optimized chromatographic conditions.

Table 1. System suitability parameters for optimized RP-HPLC method.

	R_t ± SD	A_s ± SD	N ± SD	R_s ± SD
DAPA	2.89	1.25 ± 0.03	2,207 ± 91.28	-
SITA	16.41 ± 0.07	1.64 ± 0.03	6,729 ± 253.50	25.9 ± 0.54

Figures indicated are mean of five similar determinations.
R_t = Retention time; A_s = Peak asymmetry factor; N = Number of theoretical plates; R_s = Resolution; SD = Standard deviation.

phase B. The condition its self is too complex and the flow of elution was kept at 1.5 ml/minute which gives rise to too much column back pressure. Furthermore, the major con of the reported method is that, both DAPA and SITA have the same concentration range, which is quite contrary to the fixed combination dose, and hence the newly developed method outsmarts the reported method in all the segments.

Forced degradation study

When optimized method was apllied for evaluating the stability and behaviour of active components by forced degradation study (acid hydrolysis, base hydrolysis, oxidative stress, and thermal stress), the optimized method was found to be stability indicating as it is able to separate all the degradation products in the presence of active ingridients. No degradation products found to interfere with estimation of DAPA and SITA in stressed samples (Figs. 2–4). Even the stress condition applied for the study were found to be optimim as, % degradation observed was predictive in nature (below 20%). % degradation observed for each condition is highlighted in Table 2.

Validation of analytical method

The proposed optimized RP-HPLC method was studied for validation parameters according to the ICH Q2R1 guidelines

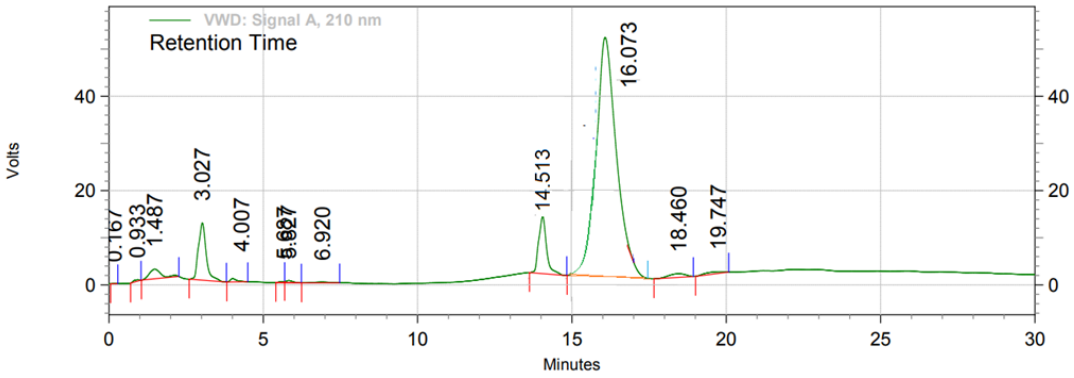

Figure 2. Chromatogram of treated sample with 0.1 N Hydrochloric acid (acid hydrolysis).

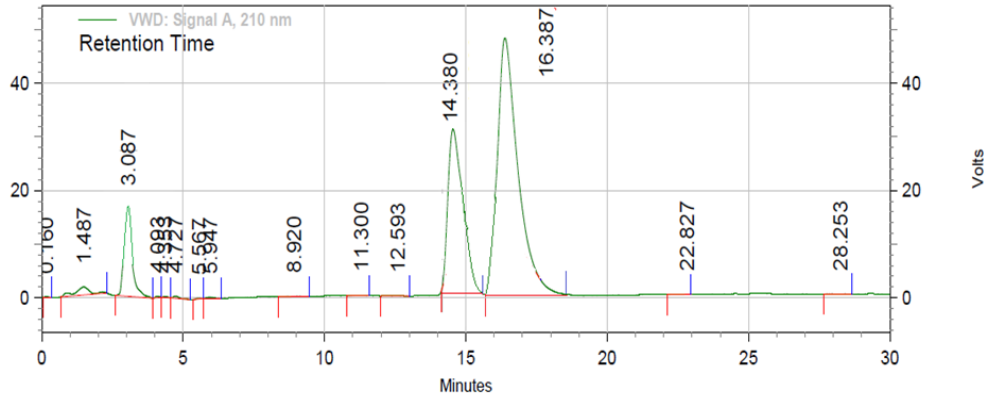

Figure 3. Chromatogram of treated sample with 0.1 N NaOH (base hydrolysis).

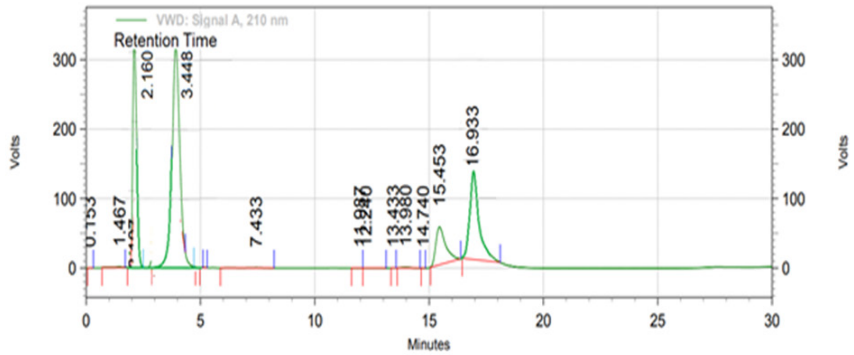

Figure 4. Chromatogram of treated sample with 3% hydrogen peroxide (oxidative stress).

Table 2. Summary of forced degradation studies.

Stress conditions	Type of sample	Area observed		% Degradation	
		DAPA	SITA	DAPA	SITA
Acid hydrolysis	0 hour sample	4,26 0,771	17,087,836	16	10
	Treated sample	3,567,915	18,986,932		
Base hydrolysis	0 hour sample	4,499,039	26,918,993	18.24	15.38
	Treated sample	3,678,030	22,778,090		
Oxidative stress	0 hour sample	40,812,761	44,860,783	12.2	22.31
	Treated sample	35,833,659	34,850,773		
Thermal stress	0 hour sample	3,060,766	45,229,827	8.03	11.24
	Treated sample	2,815,802	40,145,994		

0 hour sample = Sample prepared without imposing any stressed condition; Treated sample = sample prepared with stressed conditions.

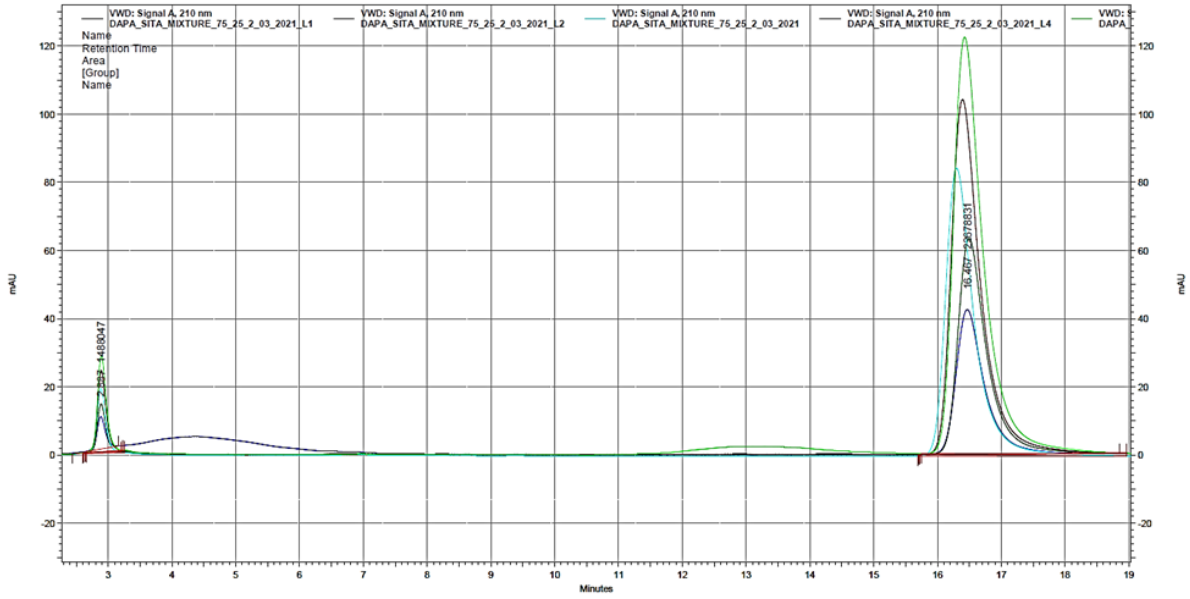

Figure 5. Overlain chromatogram of mixtures representative of linearity study.

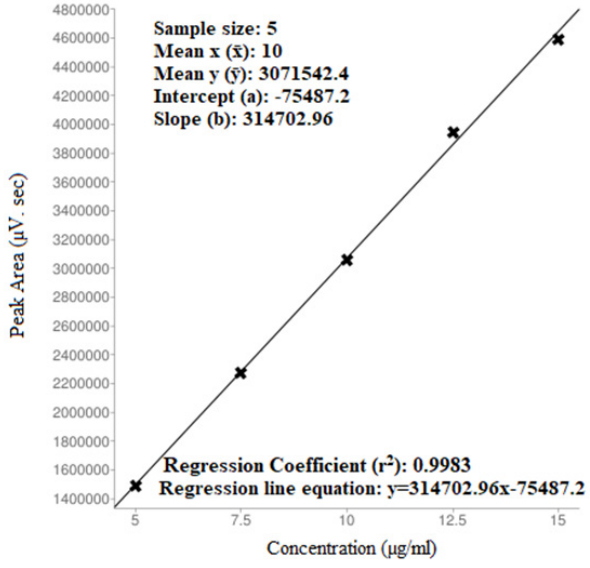

Figure 6. Regression analysis of DAPA (For linearity studies).

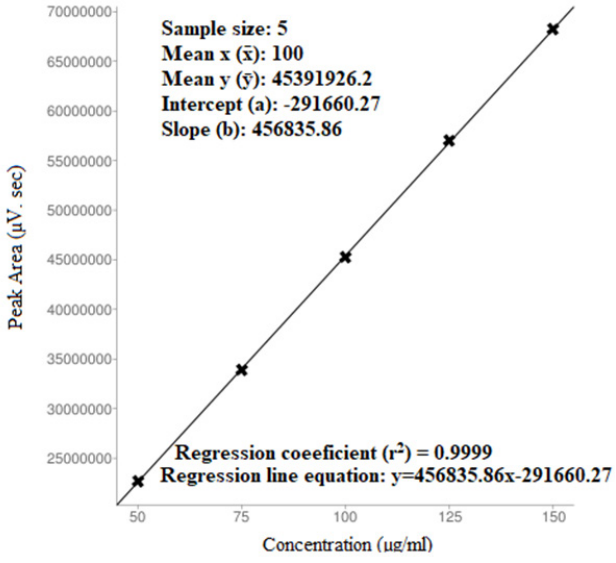

Figure 7. Regression analysis of SITA (for linearity studies).

and each validation parameter was found to be in accordance with guidelines. Method was found to be linear with linear regression co-efficient of 0.9983 and 0.999 over the range of 5–15 µg/ml of DAPA and 50–150 µg/ml SITA, respectively (Figs. 5–7). Method

Table 3. Robustness data of optimized RP-HPLC method.

Parameters	Level of changes	Observation			
		DAPA		SITA	
		Tr	Assay	Tr	Assay
Flow rate	1.1 ml/minute	2.81	99.61 ± 0.639	16.36	99.87 ± 0.842
	0.9 ml/minute	3.00	99.90 ± 0.417	16.54	99.90 ± 0.493
Temperature	28°C	2.89	99.65 ± 0.581	16.49	99.82 ± 0.430
	32°C	2.86	99.63 ± 0.134	16.44	99.61 ± 0.711
pH of mobile Phase	6.8 unit	2.89	99.81 ± 0.911	16.49	99.93 ± 0.790
	7.2 unit	2.89	99.81 ± 0.650	16.49	99.93 ± 0.832

Table 4. Ruggedness of the developed RP-HPLC method.

Change in Parameter		Result *t*-test	Inference
	Change in column		
Inertsil ODS C_{18}	Hibar ODS C_{18}	0.0068 (DAPA) 0.0094 (MON)	No significant difference

Results are mentioned at 95% confidence interval.

Table 5. Summary of validation parameters.

Parameters	DAPA	SITA
Linearity and range	5–15 µg/ml	50-150 µg/ml
Regression equation	$Y = 314{,}703 \times -75{,}487$	$Y = 456{,}837 \times -291{,}840$
Standard error (%)	75,487 (2.64%)	291,840 (0.68%)
Repeatability (RSD)	0.77–1.16	0.09–0.28
Accuracy (% recovery)	98.79–99.65	99.64–100.48
Intraday precision (RSD)	0.22–0.34	0.13–0.16
Interday precision (RSD)	0.33–0.43	0.05–0.28
Robustness	Robust	Robust
Ruggedness	Rugged	Rugged
Specificity	Specific	Specific

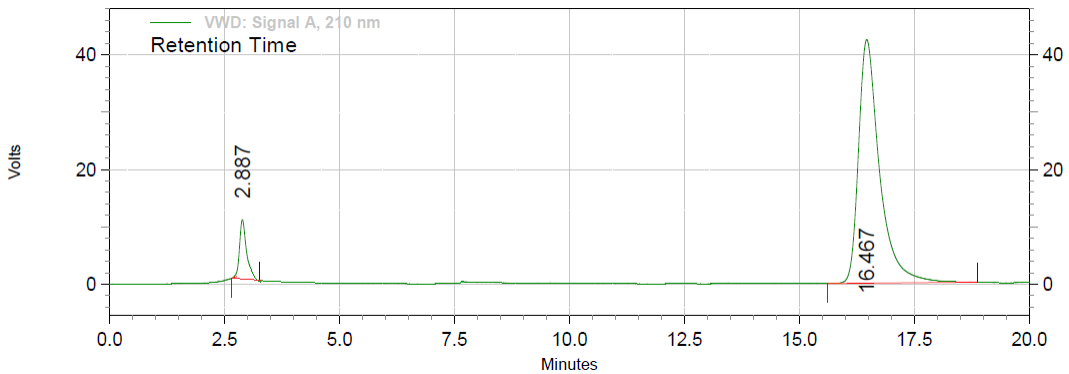

Figure 8. Assay of synthetic mixture (DAPA and SITA, 10 and 100 µg/ml, respectively).

was found to be robust and rugged as there is no significant change in results (retention time and % assay) by minor variation in method parameters, the same highlighted in Tables 3 and 4. Summary of all validation parameters is highlighted in Table 5. When optimized and validated method was applied for quantitative analysis of synthetic mixture containing DAPA and SITA (Fig. 8), the method gave accurate results with % of DAPA and SITA as 99.43 and 99.41, respectively.

CONCLUSION

As the proposed combination of DAPA and SITA is in clinical phase III, no analytical method is available yet for simultaneous quantitative expression of both the components from synthetic mixture. The proposed stability indicating RP-HPLC method not only separates and quantify the components from synthetic mixture with at most accuracy but also gives idea about the stability of mentioned components under variety of conditions as per ICHQ1 guidelines. It can be concluded that both the components are highly susceptible to oxidative stress and base hydrolysis, and hence formulation of both can be made and packaging material can be employed in such a way that it can be protected from exposure to atmospheric oxygen and exposure to moisture. Finally, method was successfully validated as per ICHQ2R1 guidelines and applied for determination of DAPA and SITA from synthetic mixture.

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CONFLICTS OF INTEREST

The authors report no financial or any other conflicts of interest in this work.

ETHICAL APPROVALS

This study does not involve experiments on animals or human subjects.

DATA AVAILABILITY

All data generated and analyzed are included within this research article.

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AUTHOR CONTRIBUTIONS

From execution of research point of view, Pinak Patel is responsible for designing of overall experiment, data acquisition, communication with team members, and preparation of manuscript along. Yesha Patel, Jigna Bhatt, and Binny Mehta are responsible for in depth review of literature and preparing each chemicals/ solution and data analysis. Krunal Detholia has a specific role to play for statistical analysis the raw data

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