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ANALYTICAL METHOD DEVELOPMENT AND VALIDATION OF CYTARABINE AND DAUNORUBICIN AND THEIR DEGRADATION STUDIES IN BULK AND FORMULATION BY UPLC

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Keywords:

Daunorubicin, Cytarabine, UPLC, Development, Validation, Stability studies

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ABSTRACT: The current investigation was Developing and validating a novel, simple, responsive, and stable UPLC method for the measurement of active pharmaceutical ingredients of Cytarabine and Daunorubicin. The chromatographic strategy utilized a phenyl column of dimensions 100 x 2.1 mm, 1.7 micron, using isocratic elution with a mobile phase of acetonitrile and 0.1 percent formic acid (70:30) with a flow rate of 0.5 ml/min and the run time is 3min and a detector wavelength of 240 nm utilizing the PDA detector was given in the instrumental settings. The Retention time (Rt) of the Cytarabine and Daunorubicin were found to be 0.164min and 1.742 min. The proposed method was validated according to an international conference on harmonization (ICH) guidelines. The accuracy results of Cytarabine and Daunorubicin were found to be 100.4% & 99.8%, and the linearity of Cytarabine and Daunorubicin were 0.992 & 0.990. Precison results of Cytarabine and Daunorubicin were 0.69 and 0.52 and the LOD and LOQ values of Cytarabine 1.65µg/ml, and 5µg/ml and Daunorubicin are 0.726µg/ml and 2.2 µg/ml. The proposed method to be used for routine analysis of production samples and to verify the quality of drug samples during stability studies.

INTRODUCTION: Cytarabine, also known as cytosine arabinoside (ara-C) and chemically it is a 4-amino-1-[(2R, 3S, 4S, 5R)-3, 4-dihydroxy-5-(hydroxymethyl) oxolan-2-yl] pyrimidin-2-one and chemotherapy medication used to treat acute myeloid leukemia (AML), acute lymphocytic leukemia (ALL), chronic myelogenous leukemia (CML), and non-Hodgkin's lymphoma [19, 20].

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It is given by injection into a vein, under the skin, or into the cerebrospinal fluid [21, 22]. There is a liposomal formulation for which there is tentative evidence of better outcomes in lymphoma involving the meninges.

Common side effects include bone marrow suppression, vomiting, diarrhea, liver problems [23, 24], rash, ulcer formation in the mouth, and bleeding. Use during pregnancy may harm the baby. Cytarabine is in the antimetabolite [25, 26] and nucleoside [27] analog families of medication.

It works by blocking the function of DNA polymerase [28, 29]. Daunorubicin, also known as daunomycin and chemically it is a (7S, 9S)-9-acetyl-7-[(2R, 4S, 5S, 6S)- 4 - amino - 5 – hydroxyl

– 6 – methyloxan – 2 -yl]oxy-6,9,11-trihydroxy-4-methoxy-8,10-dihydro-7H-tetracene-5,12-dione [1, 2] medication used to treat cancer [3, 4]. Specifically it is used for acute myeloid leukemia (AML) [5, 6], acute lymphoblastic leukemia (ALL) [7, 8], chronic myelogenous leukemia (CML) [9, 10] and Kaposi's sarcoma [11, 12]. It is used by injection into a vein. A liposomal formulation known as liposomal daunorubicin also exists. Common side effects include hair loss, vomiting, bone marrow suppression [13] and inflammation of the inside of the mouth. Other severe side effects include heart disease [14] and tissue death [15, 16] at the site of injection. Use in pregnancy may harm the baby. Daunorubicin is in the anthracycline family of medication. It partially works by blocking topoisomerase II function [17, 18]. It slows or stops the growth of cancer cells in the body.

Structures of Cytarabine and Daunorubicin:

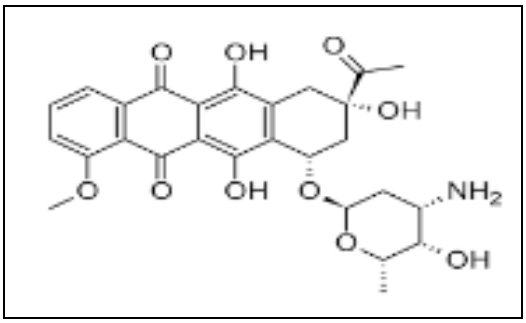

FIG. 1: DAUNORUBICIN

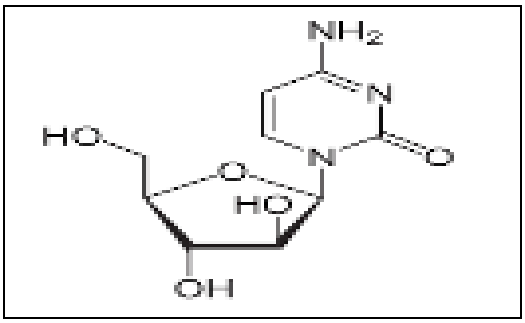

FIG. 2: CYTARABINE

MATERIALS AND METHOD:

Chemicals: Acetonitrile (HPLC grade), and formic acid water (HPLC grade) were purchased from Merck India Ltd, Mumbai, India. APIs of Daunorubicin, Cytarabine standards were procured from Glen mark, Mumbai.

The Instrumentation: Waters Acquity model UPLC with a quaternary pump, PDA detector with empower 2.0 software was used.

Chromatographic Conditions: The analysis was performed on reverse phase UPLC system with isocratic elution mode using a mobile phase of acetonitrile and 0.1% formic acid (70:30) and phenyl column of dimensions 100 x 2.1 mm, 1.7-micron column with a flow rate of 0.5 ml /min.

Diluent: Water and Acetonitrile in the ratio (50:50) is used as diluent.

Preparation of the Standard Stock Solution: For standard stock solution preparation, add 70ml of diluents to 22mg of Daunorubicin and 50 mg of Cytarabine taken in a 100 ml volumetric flask and sonicate for 10 minutes to fully dissolve the contents and then makeup to the mark with diluent. 5 ml of solution is drawn from the above normal stock solution into a 50ml volumetric flask and diluted up to the level.

Preparation of Sample Solution: Take 128 mg of the sample drug (Daunorubicin and Cytarabine) was taken into a 100 ml volumetric flask, and add 70 ml of diluents and sonicate for 10 minutes to fully dissolve the contents and then make up the mark with diluent. 5 ml of solution is drawn from the above sample stock solution into a 50ml volumetric flask and diluted up to the level this solution is filtered into a device using a 0.45µ nylon syringe in a vial.

Optimized Chromatographic Conditions: To optimize the chromatographic conditions, different ratios of acetonitrile and phosphate buffers in the mobile phase with isocratic and gradient mode was tested. However, the mobile phase composition was modified at each trial to enhance the resolution and also to achieve acceptable retention times. Finally, 0.1% formic acid buffer and acetonitrile (with isocratic elution was selected because it resulted in a greater response of active pharmacy ingredients.

During the optimization of the method, various stationary phases such as C_8, C_{18} phenyl and amino, columns were tested. From these trials, the peak shapes were relatively good, with a phenyl column of 100 x 2.1mm, 1.7 µ. The mobile phase flow rate has been done at 240nm in order to obtain enough sensitivity and the retention time found for

cytarabine and Daunorubicin are 0.864 min & 1.742 min. The standard and sample chromatograms are shown in **Fig. 3** & **4** and assay results are summarized in **Table 1**.

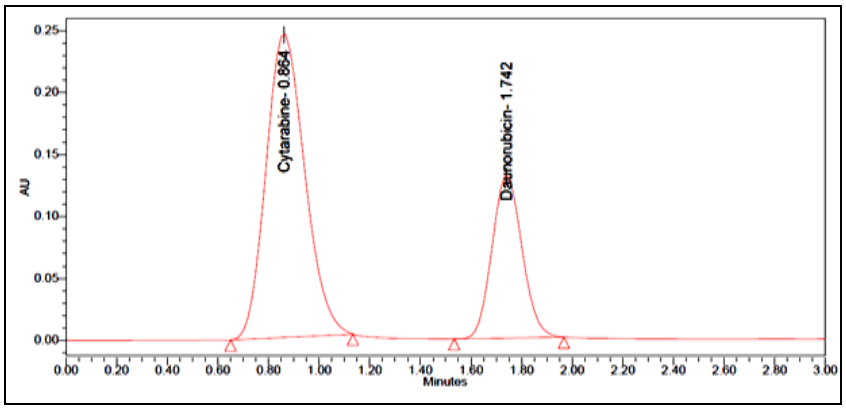

FIG. 3: STANDARD CHROMATOGRAM OF CYTARABINE AND DAUNORUBICIN

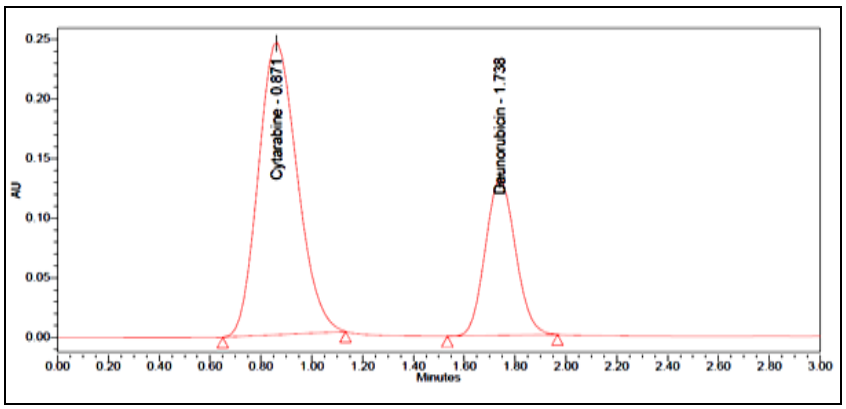

FIG. 4: SAMPLE CHROMATOGRAM OF CYTARABINE AND DAUNORUBICIN

Assy for Marketed Formulation:

TABLE 1: ASSAY RESULTS OF CYTARABINE AND DAUNORUBICIN

S. no.	Formulation	Label claim	Amount found		%Assay
1	Vyxeos (Daunorubicin and Cytarabine)	44mg/100mg per 20ml	Cytarabine	100.4mg	99.8%
			Daunorubicin	43.91mg	100.4%

RESULTS AND DISCUSSION: The main analytical challenge during developing a new method was to separate active pharmacy ingredients.

To provide good performance, the chromatographic conditions were optimized. The optimized method was validated according to ICH guidelines.

Method Validation: The analytical parameters such as system suitability, precision, specificity, accuracy, linearity, robustness, LOD, LOQ, forced degradation, and stability were validated according to ICH guidelines.

System Precision and System Suitability: System suitability parameters have been calculated to check the system's performance. The parameters can be measured and found to be within the limit, including USP plate count, USP tailing, and percent RSD. Results of system suitability and system precision were given in **Table 1** and the standard chromatogram was shown in **Fig. 5** and **Table 2.**

TABLE 2: RESULTS OF SYSTEM PRECISION AND SYSTEM SUITABILITY

S. no.	Cytarabine				Daunorubicin			
	Conc. (µg/ml)	Peak area	USP Plate Count	USP Tailing	Conc. (µg/ml)	Peak area	USP Plate count	USP Tailing
1	50	2311078	8455	1.02	22	1229082	3874	1.11
2	50	2333586	8452	1.01	22	1247503	3896	1.12

3	50	2342502	8466	1.06	22	1230656	3889	1.16
4	50	2313639	8478	1.02	22	1221863	3896	1.11
5	50	2329357	8456	1.01	22	1230588	3868	1.09
6	50	2327574	8468	0.98	22	1229914	3892	1.08
Average		2326289				1231601		
Std dev		1988.06				8471.28		
% RSD		0.515				0.688		

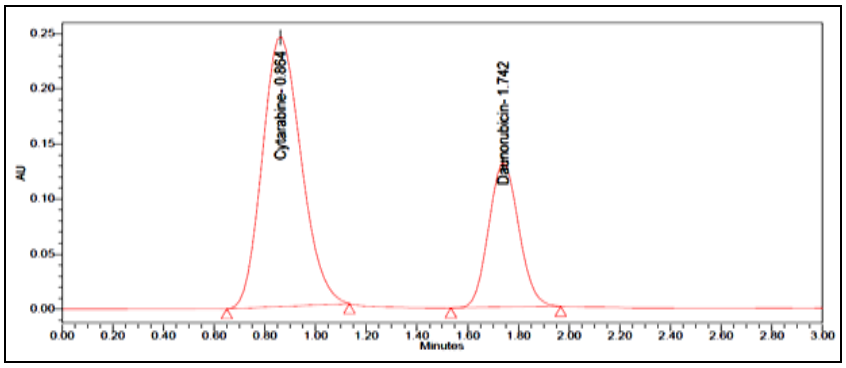

FIG. 5: CHROMATOGRAM OF SYSTEM SUITABILITY

Specificity:

Placebo Interference: The capacity to test the analyte unequivocally in the presence of other elements, such as impurities, and Excitements that might be assumed to be present in the sample solution and norm solution, is specificity. According to the test method placebo, sample and standard solutions were analyzed individually to examine the interference. The figure below shows that the active ingredients were well separated from blank and their excipients and there was no placebo interference with the principal peak. Hence the method is specific. The specificity results were summarized in **Tables 3** & **4,** and chromatograms are shown in **Fig. 6-14.**

TABLE 3: RESULTS OF PLACEBO INTERFERENCE

Sample name	Peak Found
Blank	NO
Placebo	NO
Cytarabine	0.864
Daunorubicin	1.742

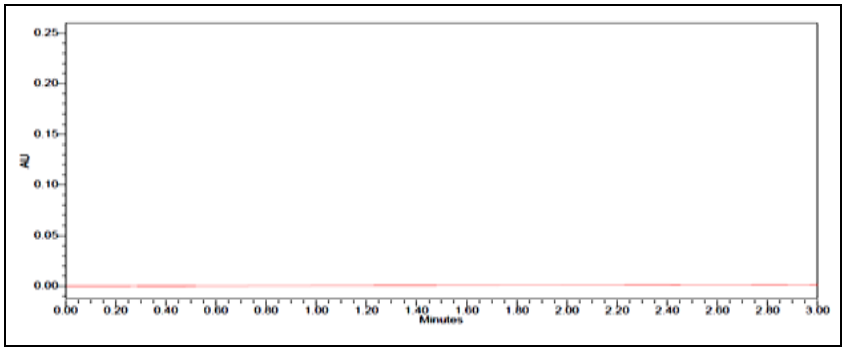

FIG. 6: CHROMATOGRAM OF BLANK

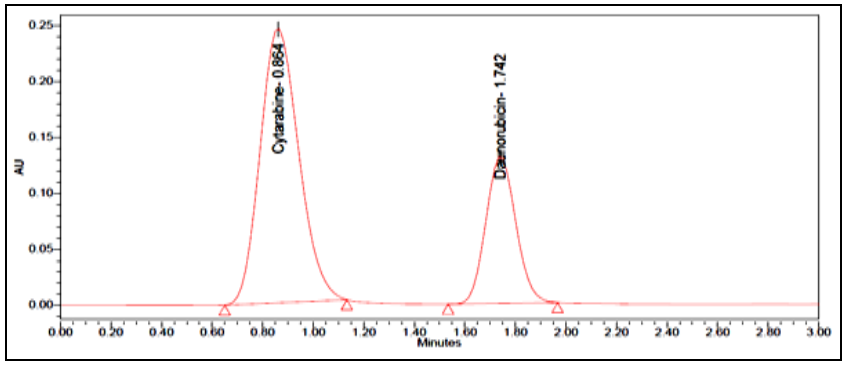

FIG. 7: CHROMATOGRAM OF STANDARD

Forced Degradation Studies: The Cytarabine and Daunorubicin sample was subjected into various forced degradation conditions to effect partial degradation of the drug.

Studies of forced degradation have been carried out to determine whether the method is suitable for degradation products.

In addition, the studies provide details about the conditions during which the drug is unstable, in order that measures are often taken during formulation to avoid potential instabilities.

Sample Stock Solution Preparation: Take 128 mg of the sample drug (Daunorubicin and Cytarabine) was taken into a 100 ml volumetric flask, and add 70 ml of diluents and sonicate for 10 minutes to fully dissolve the contents and then make up the mark with diluent.

5 ml of solution is drawn from the above sample stock solution into a 50ml volumetric flask and diluted up to the level.

Acid Degradation: 1 ml of sample stock solution is passed on to a volumetric flask of 10 ml, 1 ml of 1N HCl and leaves it for 15 min. After 15 min add 1 ml of 1N NaOH and made up to the mark with diluents.

Alkali Degradation: 1 ml of sample stock solution was put in a 10 ml volumetric flask and add 1 ml of 1N NaOH and leave it for 15 min. After 15 min add 1 ml of 1N HCl and made up to the mark with diluents.

Peroxide Degradation: In a 10 ml volumetric flask, 1 ml of sample stock solution was transferred, add 0.3 ml of 30% hydrogen peroxide and made up to the mark with diluents.

Reduction Degradation: In a 10 ml volumetric flask, 1 ml sample stock solution was transferred and add 1 ml of 30% sodium bisulphate solution and made up to the mark with diluents.

Thermal Degradation: The sample stock solution was set in an oven at 105^{o} for 6 hours. The resultant solution was injected into UPLC.

Hydrolysis Degradation: In a 10 ml volumetric flask, 1 ml sample stock solution was transferred, and add 1 ml of UPLC water and made up to the mark with diluents.

TABLE 4: FORCED DEGRADATION RESULTS OF CYTARABINE AND DAUNORUBICIN

Degradation condition	Cytarabine				Daunorubicin			
	%Assay	%Degradation	Purity angle	Purity threshold	% Assay	%Degradation	Purity angle	Purity Threshold
Control	100	0	10.457	40.478	100	0	5.091	21.263
Acid	87.1	12.9	10.364	40.421	86.3	13.7	5.084	21.367
Base	88.8	11.2	10.314	40.341	87.6	12.4	5.077	21.054
Peroxide	86.2	13.8	10.261	40.261	84.1	15.9	5.061	21.221
Reduction	89.3	10.7	10.251	40.185	88.6	11.4	5.064	21.362
Thermal	95.9	4.1	10.213	40.143	96.2	3.8	5.032	21.395
Hydrolysis	97.1	2.9	10.154	40.121	99.9	2.1	5.028	21.749

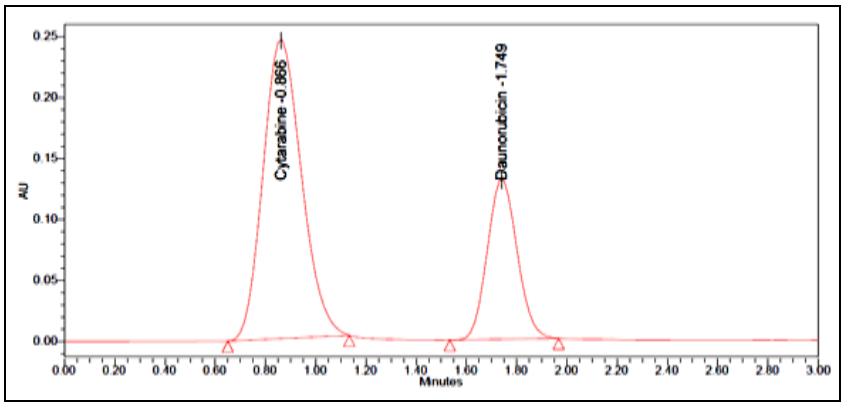

FIG. 8: CONTROL DEGRADATION CHROMATOGRAM

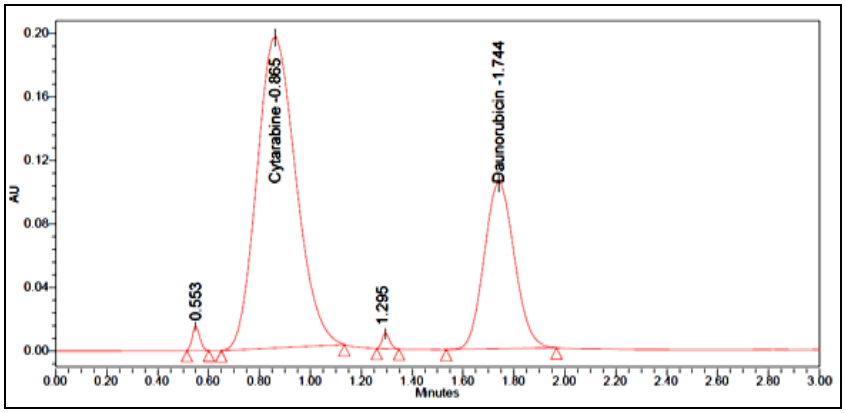

FIG. 9: ACID DEGRADATION CHROMATOGRAM

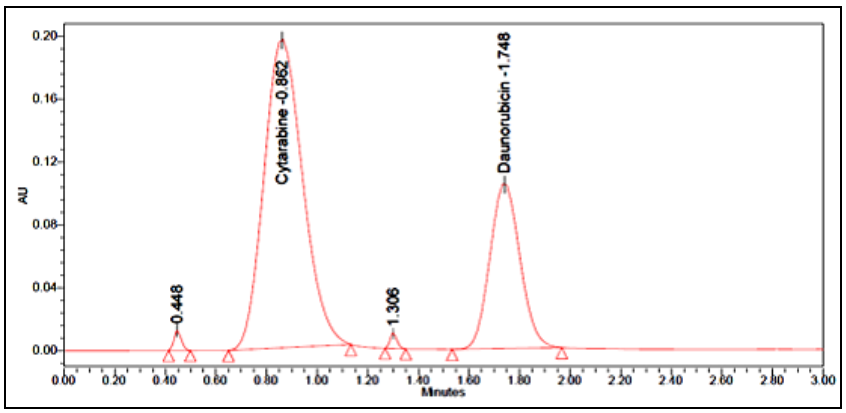

FIG. 10: ALKALI DEGRADATION CHROMATOGRAM

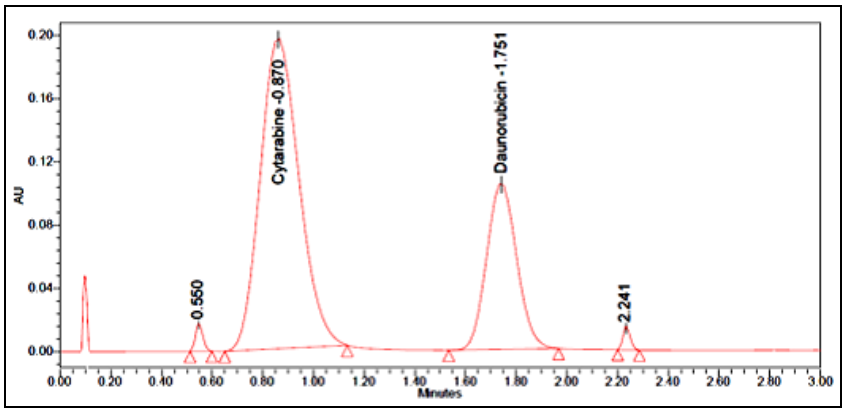

FIG. 11: PEROXIDE DEGRADATION CHROMATOGRAM

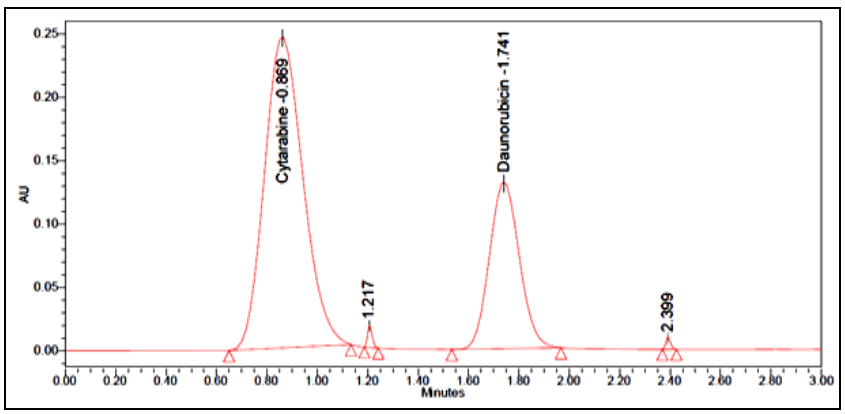

FIG. 12: REDUCTION DEGRADATION CHROMATOGRAM

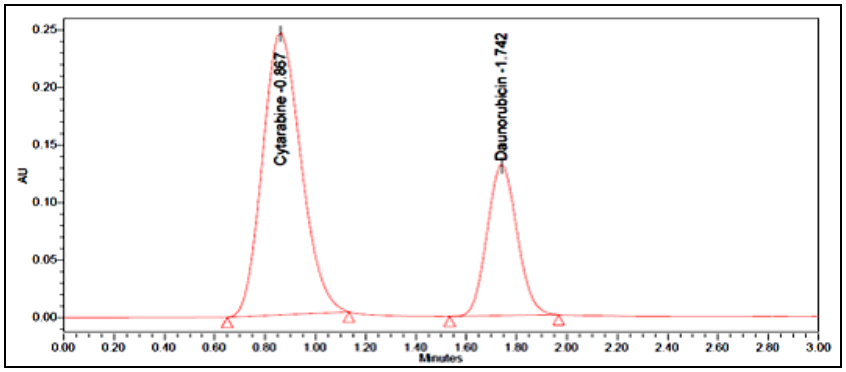

FIG. 13: THERMAL DEGRADATION CHROMATOGRAM

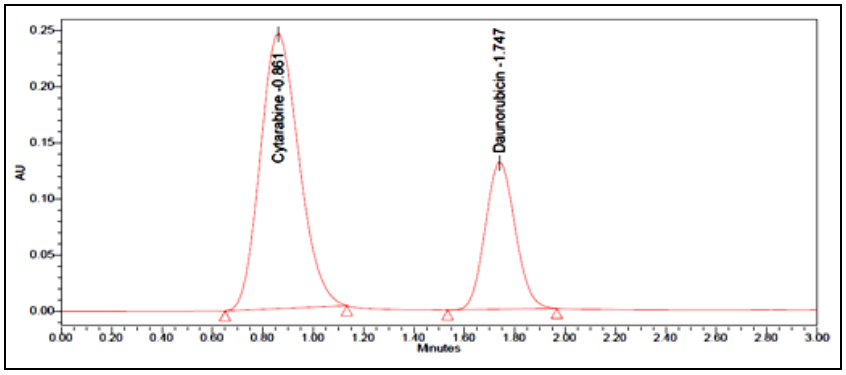

FIG. 14: HYDROLYSIS DEGRADATION CHROMATOGRAM

Linearity: The area of the linearity peak versus different concentrations has been evaluated for Daunorubicin, Cytarabine, as 25, 50, 75, 100, 125, 150 percent respectively. The linear regression analysis was plotted with the peak area versus concentration data. The correlation coefficients of regression, Percenty-intercept, and slope of the calibration curves were calculated. The correlation coefficients achieved greater than 0.999 for all. The Calibration plots are shown in **Fig. 15** & **16,** and the Linearity results are summarized in **Table 5.**

TABLE 5: LINEARITY OF DAUNORUBICIN AND CYTARABINE

S. no.	Concentration(µg/ml)	Peak area of Cytarabine	Concentration(µg/ml)	Peak area of Daunorubicin
1	12.50	684515	5.50	304895
2	25.00	1124575	11.00	674526
3	37.50	1727484	16.50	958347
4	50.00	2344563	22.00	1212478
5	62.50	2945894	27.50	1592594
6	75.00	3565436	33.00	1924456
Correlation coefficient(R^2)		0.99925		0.99903
Slope		46968.73		57705.96
intercept		9025.21		322.50

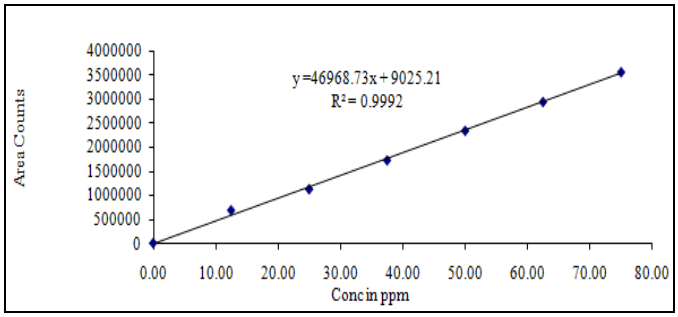

FIG. 15: CALIBRATION PLOT OF CYTARABINE

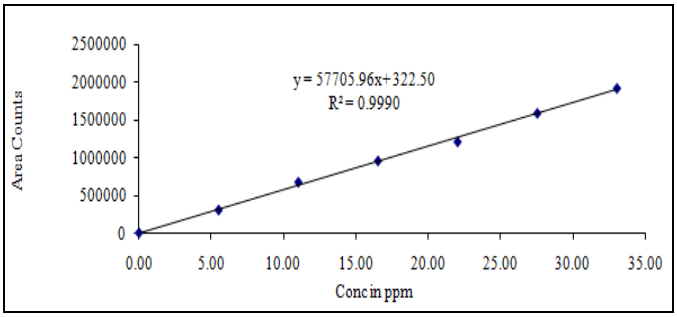

FIG. 16: CALIBRATION PLOTS OF DAUNORUBICIN

Accuracy: In this method, accuracy was conducted in triplicate by analyzing active pharmaceutical ingredients with equivalent amount of placebo at three concentration levels of 50, 100 and 150% of each at a specified limit. The %Recovery was found to be within limits. The results are given in **Table 6,** and the chromatograms are shown in **Fig. 17, 18, 19.**

TABLE 6: RECOVERY RESULTS OF CYTARABINE AND DAUNORUBICIN

	Cytarabine				Daunorubicin			
Spiking level (%)	**Amount of API added (ppm)**	**Amount of API found (ppm)**	**%Recovery**	**% Mean recovery**	**Amount of API added (ppm)**	**Amount of API found (ppm)**	**%Recovery**	**%Mean recovery**
50	25.00	24.59	98.4	99.7	11.00	10.98	99.8	100
	25.00	25.3	101.2		11.00	11.16	101.5	
	25.00	24.86	99.4		11.00	10.85	98.6	
100	50.00	50.41	100.8	100.5	22.00	21.66	98.5	99.8
	50.00	49.65	99.3		22.00	22.18	100.8	
	50.00	50.62	101.2		22.00	22.08	100.1	
150	75.00	76.34	101.8	101.2	33.00	33.06	100.2	100.4
	75.00	75.9	101.2		33.00	32.79	99.4	
	75.00	75.5	100.7		33.00	33.58	101.8	

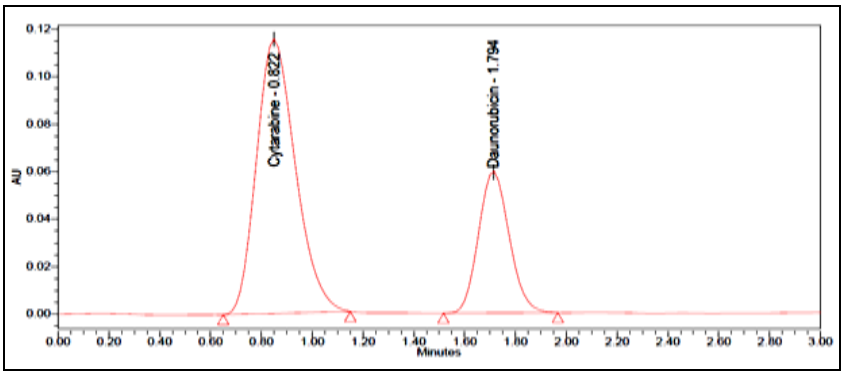

FIG. 17: CHROMATOGRAM FOR ACCURACY AT 50% SPIKE LEVEL

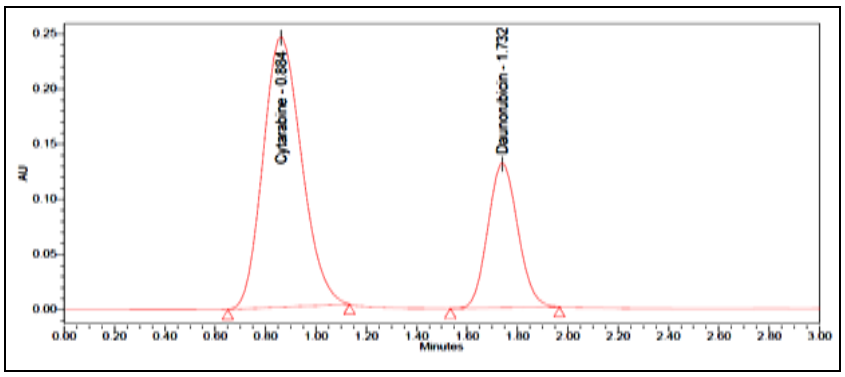

FIG. 18: CHROMATOGRAM FOR ACCURACY AT 75% SPIKE LEVEL

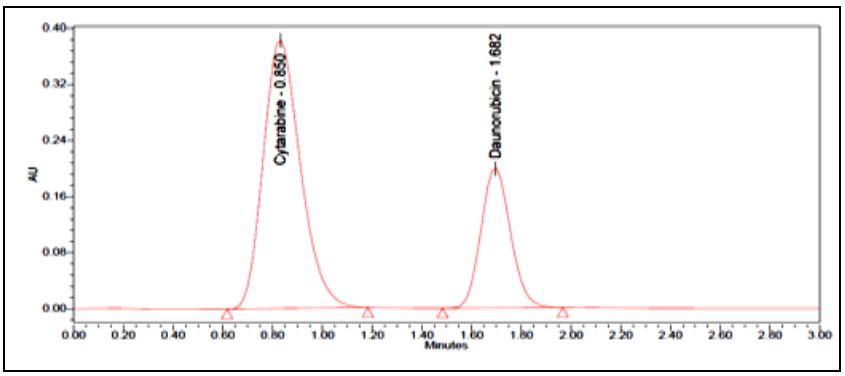

FIG. 19: CHROMATOGRAM FOR ACCURACY AT 100% SPIKE LEVEL

Precision:

Method Precision: The precision of an analytical technique is the degree of closeness of a series of measurements from samplings. The exactness of the process of related substances was performed by injection of six individual injection determinations of Cytarabine (50ppm) and Daunorubicin (22ppm) and. Intraday precision results were given in **Table 7** and the sample chromatogram was shown in **Fig. 13.**

TALE 7: METHOD PRECISION RESULTS OF CYTARABINE AND DAUNORUBICIN

S. no.	Cytarabine			Daunorubicin		
	Conc.(µg/ml)	Area counts	% Assay	Conc.(µg/ml)	Area counts	% Assay
1	50	2348714	101	22	1251871	101.6
2		2317242	99.6		1214952	98.6
3		2328741	100.1		1229874	99.9
4		2344578	100.8		1232478	100.1
5		2365719	101.7		1209736	98.2
6		2309417	99.3		1241897	100.8
	Mean		100.4			99.9
	SD		0.911			1.289
	%RSD		0.91			1.29

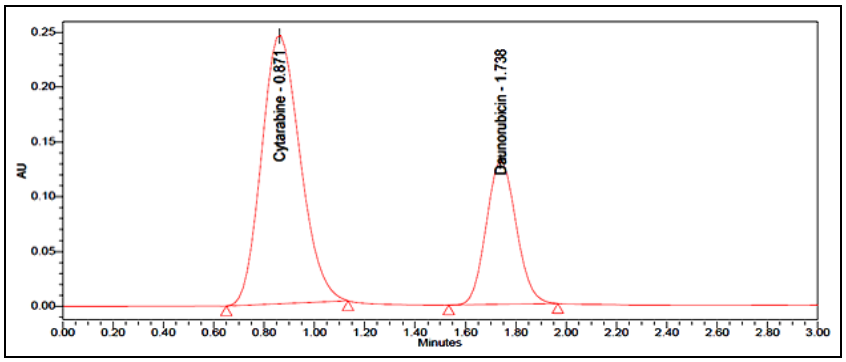

FIG. 20: CHROMATOGRAM FOR METHOD PRECISION

Intermediate Precision: Six replicates of the sample solution were studied by different analysts different days and different instruments were tested. The peak regions used to determine to mean percent RSD values have been calculated. The results are given in the following **Table 8.**

TABLE 8: INTER-DAY PRECISION OF DAUNORUBICIN AND CYTARABINE

S. no.	%Assay for Cytarabine		% Assay for Daunorubicin	
	Day-1	Day-2	Day-1	Day-2
1	101	100.8	101.6	100.3
2	99.6	99.4	98.6	101.9
3	100.1	99.0	99.9	99.4
4	100.8	98.1	100.1	99.1
5	101.7	101.6	98.2	101.0
6	99.3	101.2	100.8	100.6
Average	100.4	100.4	99.9	100.2
SD	0.911	1.027	1.289	1.323
%RSD	0.91	1.02	1.29	1.32

Detection Limit and Quantification Limit: LOD and LOQ were calculated separately using the calibration curve process. The LOD and LOQ of the compound were calculated using the developed UPLC method by injecting increasingly lower concentrations of the standard solution. The LOD and LOQ concentrations and their S/N values were shown in the following **Table 9.**

TABLE 9: LOD AND LOQ FOR CYTARABINE AND DAUNORUBICIN

Cytarabine				Daunorubicin			
LOD		LOQ		LOD		LOQ	
Concentration	s/n	Concentration	s/n	concentration	s/n	Concentration	s/n
0.75µg/ml	5	5µg/ml	26	1.65µg/ml	4	2.2µg/ml	23

Ruggedness:

Analyst to Analyst/System to System/Column to Column: Ruggedness of the assay method was conducted by using different systems by different analysts using different columns and analyzed under similar conditions as per the test method. The results are summarized in **Table 10.**

TABLE 10: RUGGEDNESS RESULTS FOR ANALYST-1 TO ANALYST-2

S. no.	System suitability	Observed value		Acceptance criteria
		Analyst-1	Analyst-2	
1	% RSD of Cytarabine	0.57	1.29	NMT 2.0 %
2	Tailing factor for Cytrabine	1.05	1.25	NMT-2.0
3	% RSD for Daunorubicin	0.69	1.32	NMT-2.0%
4	Tailing factor for Daunorubicin	1.00	1.16	NMT-2.0

Stability: The sample solution was kept at room temperature and at 2-8^{o}C for 24 hours. Then these solutions were pumped into the device, and calculate the % of deviation was from initial to 24 hrs. There was no significant deviation observed, and it confirmed that the solutions were stable up to 24 his percentage of the assay was not quite 2%. There is no effect in storage conditions for Cytarabine and Daunorubicin drugs. Stability results were shown in **Tables 11** & **12.**

TABLE 11: BENCH TOP STABILITY RESULTS AT ROOM TEMPERATURE

Stability	Daunorubicin		Cytarabine	
	% Assay of test preparation	% Difference	Purity	% Difference
Initial	100	0.00	100	0.00
6 Hrs	99.5	0.50	99	1.00
12 Hrs	98.8	1.20	98.8	1.20
18 Hrs	97.9	2.10	98	2.00
24 Hrs	97.4	2.60	97.4	2.60

TABLE 12: REFRIGERATOR STABILITY RESULTS AT 2-8°C

Stability	Daunorubicin		Cytarabine	
	Purity	% Difference	Purity	% Difference
Initial	100	0.00	100	0.00
6 Hrs	99.4	0.60	99.6	0.40
12 Hrs	99	1.00	98.7	1.30
18 Hrs	98.7	1.30	98.3	1.70
24 Hrs	98.2	1.80	97.6	2.40

Robustness: The conditions of the experiment were designed to test the robustness of established systems intentionally altered, such as flow rate, and mobile phase composition in all these varied conditions. The resolution between active pharmaceutical ingredients was not significantly affected, and there was no significant influence on the time of retention, plate count, and tailing factor. Hence this method was robust. Robustness results were summarized in **Table 13.**

TABLE 13: ROBUSTNESS DATA OF CYTARABINE AND DAUNORUBICIN

Parameter name	% RSD		Tailing factor	
	Cytrabine	Daunorubicin	Cytrabine	Daunorubicin
Flow minus (0.8 ml/min)	0.17	0.51	1.15	1.07
Actual Flow rate (1ml/min)	0.51	0.688	1.16	1.06
Flow plus (1.2 ml/min)	1.2	0.4	1.14	1.08
Organic phase composition minus (-10%)	1.16	1.13	1.19	1.16
Actual organic phase composition	0.51	0.68	1.16	1.06
Organic phase composition plus (+10%)	1.11	1.5	0.9	1.11

CONCLUSION: This article presents simple, selective, validated, and well-defined stability that shows isocratic RP-UPLC methodology for the quantitative determination of Cytarabine and Daunorubicin. All the degradation products formed during the stress conditions are well separated, and peaks were well resolved from each other and separated with an appropriate retention time

indicating that the proposed method is fast, simple, feasible, and affordable in assay conditions. Therefore, the developed method during stability tests can be used for routine analysis of production samples and to verify the quality of drug samples during stability studies.

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