QUANTIFICATION OF RANOLAZINE AND DRONEDARONE BY STRONG CATION EXCHANGE CHROMATOGRAPHY

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ABSTRACT

The objective of this study was to validate first non-C18 column estimation of Ranolazine and Dronedarone using Ion Exchange Chromatography. The method was validated as per the International Council for Harmonisation (ICH) guidelines by using paremeters like Precision, Linearity, Range, Robustness, Limit of Detection (LOD) and Quantification (LOQ), along with degradation studies. As a result, the simultaneous estimation successfully distinguished between Ranolazine and Dronedarone at wavelengths of 240 and 280 nm, with resolution (R) and capacity factor (k) which were both within acceptable ranges. Thus, UltraSil-MCX column eluent compositions, buffers, and elution modes were explored to increase specificity and selectivity. Isocratic elution with 10mM ammonium formate (AF)-methanol (22:78 *v/v*) yielded the best results. Ranolazine and Dronedarone absorb best at 240 nm and 280 nm, respectively, hence UV detection was done at those wavelengths. From results obtained; it is concluded that the the proposed method is validated as per the guidelines.

Keywords: Ranolazine, Dronedarone, Ion exchange chromatography, Forced degradation study

Introduction

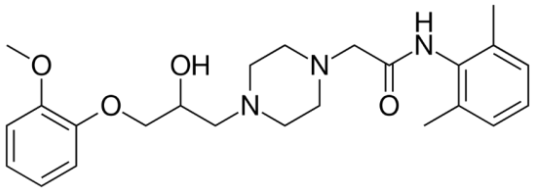
Pharmaceutical analysis is a subfield of analytical chemistry that entails a series of procedures for separating substances in a solution or mixture, identifying and quantifying substances, and elucidating the structures of chemical compounds [1]. It doesn't matter what shape the chemical takes, it could be a single compound or a combination of compounds. Animals, plants, microbes, minerals, and synthetic items are all utilised in the pharmaceutical industry. During the process of developing and producing pharmaceuticals, these analytical techniques are well suited for the job [2]. The pharmaceutical industry must have a comprehensive validation policy outlining the process of validation if it is to meet GMP standards [3]. Analytical monitoring of the product or its ingredients is required to guarantee the safety, efficacy, and clinical relevance of a drug product during its entire shelf life, from manufacturing to storage to distribution. This method is used to determine the chemical composition of a substance and to isolate its active ingredients from a solution or mixture. The primary goals of pharmaceutical analysis are quality control and efficacy evaluation. Also included are numerical values and a succinct description of the medicine in question. There would be no drug evolution or discovery without the contributions of pharmaceutical analysis. Analytical techniques are used to perform quantitative and qualitative evaluations of pharmaceutical formulations. Various techniques are used for the determination of the concentration of a compound; these techniques are titration, spectroscopy, chromatography, and gravimetric analysis.

Previous research articles have reported on the simultaneous analysis of these two drugs; however, none have disclosed their sensitivity when using UV detection. Additionally, the reported methods employed complex elution techniques, resulting in lengthy analysis times and increased solvent consumption [4-6]. Therefore, the primary objective of this paper is to provide readers with guidance on achieving optimal conditions for High-Performance Liquid Chromatography (HPLC). The steps involved in developing a new analytical methodology and analytically validating with proper quantification of Ranolazine and Dronedarone by

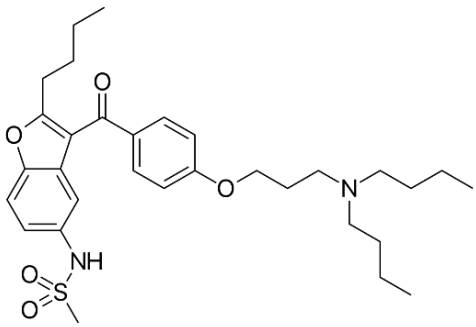
strong cation exchange chromatography.

Ranolazine **Fig. 1(a)** is chemically N-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy)propyl]piperazin-1-yl] acetamide used as antianginal agent. It inhibits persistent or late inward sodium current (INa) in the heart muscle. Inhibiting the current leads to reductions in intracellular calcium levels. This leads to reduced tension in the heart wall, leading to reduced oxygen requirements for the muscle. [7,8]

Dronedarone **Fig. 1(b)** is chemically N-(2-Butyl-3-(*p*-(3-(dibutylamino)propoxy)benzoyl)-5-benzofuranyl) methanesulfonamide used as an anti-arrhythmic drug. It has been termed a "multichannel blocker". [9,10] However, it is unclear which channel(s) play a pivotal role in its success. Thus, dronedarone's actions at the cellular level are controversial, with most studies suggesting an inhibition in multiple outward potassium currents including rapid delayed rectifier, slow delayed rectifier and ACh-activated inward rectifier. It is also believed to reduce inward rapid Na current and L-type Ca channels. [11]



(a)



(b)

Fig. 1 Structure of (a) Ranolazine and (b) Dronedarone

MATERIALS AND METHODS

Apparatus

HPLC system

The High-Performance Liquid Chromatography (HPLC) of Shimadzu SCL-10AVP inbuilt with a binary pump (LC-10ATVP), UV detector (SPD-10AVP), Rheodyne 20 µl loop capacity manual injector (P/N 77251) was used throughout the analysis. The LC-Solution software was used to interpret the HPLC reports. UltraSil-MCX®, 5µm; 100 x 2.1mm ID., column purchased

from (Newcastle-UK) was used throughout the analysis. Digital weighing balance (ME-204) purchased from Mettler-Toledo (USA), ultra-sonicator Labman® purchased from UltraChrom Ltd, India. A digital pH meter from Mettler-Toledo was purchased from (Mumbai-India). A 50 µ micro-syringe was purchased from Hamilton USA. 0.20 µ and 0.45 µ nylon membrane filters were purchased from Phenomenex® Mumbai, India.

Chemicals and reagents

All HPLC-grade chemicals and solvents were purchased from Merck (Mumbai, India).

Chromatographic conditions

HPLC analysis was performed on the Shimadzu HPLC system. Mobile phases A and B were water and methanol, respectively. Both contained 15 mM ammonium formate (AF). Ranolazine and Dronedarone were eluted with 15mM ammonium formate-methanol (22:78 *v/v* for 8 min with considering isocratic elution at 1.2 ml/min flow rate. All separations were performed at 28°C and recorded at wavelength 280 nm for Ranolazine and 240 nm for Dronedarone.

Preparation of analytical solutions

Standard preparation

Standard stock solutions of Ranolazine and Dronedarone (1 mg/ml) were prepared separately by dissolving 100 mg of the drug in methanol-water (2:1 *v/v*) completing the final volume by adjusting with either methanol or water, based on their solubility in particular solvents up to 100 ml. Furthermore, the freshly prepared sample solution was sonicated for 10-20 min and filtered through 0.20 µ nylon filters. Required serial dilution was made for evaluating the validation studies [12].

Sample preparation

The working stock solution of Ranolazine and Dronedarone (100 µg/ml) was prepared by diluting 10 ml of the standard solution into 100 ml of the mobile phase. Further serial dilutions were made and then developed SCX-HPLC methods were evaluated for Ranolazine and Dronedarone [12].

Method validation procedures

Precision

Precision results were expressed in Relative Standard Deviation (RSD). In repeatability, a standard stock solution of both Ranolazine and Dronedarone (100 µg/ml) was injected six times a day and their resultant peak areas and RSD were determined. Similarly, in intraday and intermediate precision, (three different days) a standard stock solution containing 100 µg/ml of Ranolazine and Dronedarone was injected thrice and their respective RSD were calculated [13].

Linearity and range

Linearity was determined by using the calibration curve of Dronedarone and Ranolazinein the range of the concentration between 100 and 6.25 µg/ml (100, 50, 25, 12.5, 6.25 µg/ml). Before that, both standards Dronedarone and Ranolazine were independently dissolved in 15 Mm AF-MeOH eluent to make the concentration of 1 mg/ml and then they were mixed and diluted with the same eluent to obtain the serial dilutions. The linearity of the peak area against the concentration was calculated to get regression values and correlation coefficient (r^2) [14].

Limit of detection (LOD) and quantification (LOQ)

The limit of detection **(**LOD) and quantification (LOQ) was determined by injecting the homologous mixture of Ranolazine and Dronedarone standard solutions in the range of 100 and 6.25 µg/ml. Furthermore, the LOD and LOQ were calculated using the following formula: [15]

$$\text{LOD} = 3.3 \times \frac{\text{Std. Deviation of intercept}}{\text{Slope}}$$

$$\text{LOQ} = 10 \times \frac{\text{Std. Deviation of intercept}}{\text{Slope}}$$

Robustness

The robustness studies involved the small variations in selected separation parameters such as changes in flow rate (±0.2 ml/min), concentration of organic modifier (±2 ml) and temperature (±2°C) were tested and evaluated. The flow rate of the eluent was changed from 1.2 ml/min to

1 and 1.4 ml/min; the concentration of organic modifier was changed from 80% to 78% and 82% and the temperature was changed from 32^0C to 30^0C and 34^0C. Furthermore, the results derived were evaluated for any changes in capacity factor (k'), resolution (R), theoretical plates (N), and tailing factor (T) [15].

Degradation studies

Acid, alkali, oxidation and thermal degradation studies

Forced degradation studies of Ranolazine and Dronedarone were performed as per the International Council for Harmonization (ICH) guideline [16]. 8 ml of a freshly prepared homologous mixture of stock solution, containing Ranolazine and Dronedarone (100 µg/ml) prepared in H_2O–methanol eluents were equally distributed into 4 different 25 ml volumetric flasks and further diluted with an equal volume of H_2O, 0.1 N HCl, 0.1N NaOH, and 3% H_2O_2 to get a final concentration of 25 µg/ml Ranolazine and Dronedarone respectively.

The sample prepared in 3% H_2O_2 was kept at room temperature for 6 hours whereas the acid-base and neutral hydrolyzed samples were kept at 60°C for 6 hours. Furthermore, all samples were sonicated, and filtered through 0.20 µ nylon filters and then 20 µl of each sample was analysed by HPLC using the specified chromatographic method mentioned in the chromatographic condition.

RESULT AND DISCUSSION

It is the first simultaneous estimation of Ranolazine and Dronedarone attempted other than the conventional C18 column. Ion Exchange Chromatography (IEC) was comprehensively used for a simultaneous investigation of both Ranolazine and Dronedarone with good resolution, selectivity and sensitivity. Importantly, several research articles have reported the simultaneous analysis of both Ranolazine and Dronedarone. However, no one has disclosed their sensitivity to UV detection. Moreover, the reported methods were found somewhat complicated since they used the complex elution technique to achieve the simultaneous estimation of both selected drugs [4-6]. Moreover, their total analysis time was quite elongated which practically increases the time for analysis and solvent consumption. Therefore, this simultaneous estimation

demonstrated successfully the separation of Ranolazine and Dronedarone with appropriate resolution (R) and capacity factor (k) and greatly enhanced UV sensitivity performed at 240 and 280 nm wavelengths. It just took 8 minutes to completely separate the two. The result was shown in **Fig.2**. Therefore, to improve the specificity and selectivity various eluent compositions, buffers selection and elution modes were tested and evaluated on the UltraSil-MCX column. Finally, separation was carried out using isocratic elution consisting of 10mM ammonium formate (AF)- methanol (22:78 *v/v*) explicit best results. Ranolazine and Dronedarone UV detection was performed at 240 nm and 280 nm, respectively, because these are the wavelengths at which the compounds absorb the most UV light. To improve resolution and peak symmetry, the flow rate was lowered to 1.2 ml/min.

The primary goal of this paper is to assist the reader in achieving optimal HPLC conditions. The steps involved in creating a new methodology and validating it analytically are laid out here.

Hence, the proposed HPLC method for quantifying Ranolazine and Dronedarone simultaneously was validated as per ICH guidelines [16]. Besides testing the system's appropriateness, researchers also looked at its linearity, accuracy, precision (intra/intermediate), robustness, and specificity. As can be seen in **Table 1**, the system suitability characteristics of the proposed HPLC approach exhibit a high degree of reproducibility for the simultaneous quantification of Ranolazine and Dronedarone. The suggested approach yielded a mean k' of 1.52 and a mean t_R of 1.33 for Ranolazine, while the corresponding values for Dronedarone were 2.44 and 3.34, respectively (**Table 2**). T values less than 2 indicated that neither analyte exhibited any detectable tailing. If the symmetric and asymmetric factors were equally large for both compounds, the peak would be a perfect Gaussian. Both Ranolazine and Dronedarone had separation factors (α) and resolutions (R_s) well above the ICH rules bare minimum. [16].

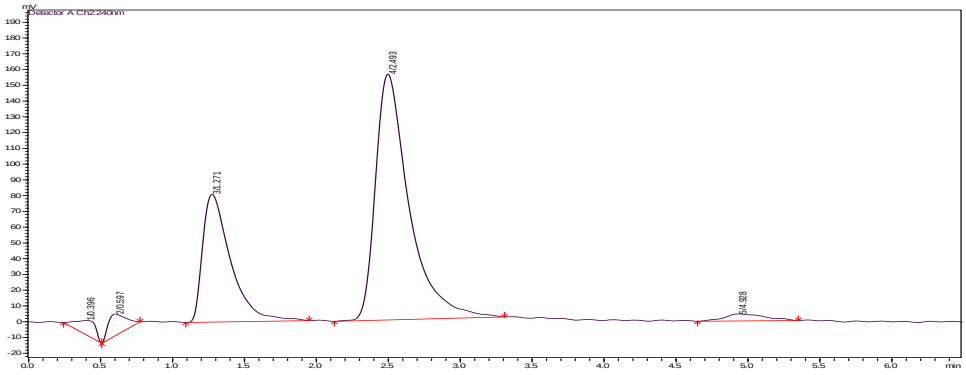


Fig.2: Ranolazine and dronedarone with 15mM AF-MeOH (22:78 *v/v*)

Table 1: Retention parameter of ranolazine and dronedarone

Peak#	Retention Time	Area	Area%	T. Plate#	Resolution	k'	Tailing Factor	Separation
1	0.396	85841	2.1847	40.622	--	0	0.849	0
2	0.597	120334	3.0626	99.436	0.828	0.51	1.533	0
Ranolazine	1.271	1098108	27.9476	217.867	2.305	2.212	1.35	4.334
Dronedarone	2.493	2535811	64.5382	616.302	3.277	5.302	1.45	2.397
impurity	4.928	89067	2.2668	1781.829	5.607	11.459	1.296	2.161

Method validation

Method validation was performed as per ICH standards [16].

Table 2: System suitability of ranolazine and dronedarone

System Suitability Parameters	Ranolazine	Dronedarone	Acceptable Values
Theoretical plates (*N*)	219	613	**> 2000**
Capacity Factor (*K'*)	2.13	5.15	**> 1.5 - <10**
Resolution (*R*)	---	3.27	**≥ 2**
Selectivity/Separation factor (α)	4.64	2.41	**>*k'***
Asymmetry/Tailing factor (*T*)	1.45	1.29	**> 2**
Retention time (t_R)	1.27 min.	2.49 min.	**> *k'***
Wavelength of Detection (nm)	240 nm	280 nm	**> 200 nm**
Repeatability (%RSD)	1.91%	1.20%	**< 2**
Intra-Day Precision (%RSD)	0.44 – 1.62	0.35 -0.87	**< 2**
Inter-Day Precision (%RSD)	0.26 – 1.61	0.87 – 1.52	**< 2**
Linearity range	3.9 – 250 µg/ml	7.8 – 250 µg/ml	**NA**
Regression equation	Y= 47867x + 27624	Y= 29619x + 3788.5	**NA**
SE of intercept (S_e)	3177.71	13573.8	**NA**
SD of intercept (S_a)	7105.57	33248.88	**NA**
Correlation Coefficient (r^2)	0.9999	0.9999	**NA**
LOQ[a] (µg/ml)	12.04 µg/ml	11.22 µg/ml	**NA**
LOD[a] (µg/ml)	3.97 µg/ml	3.70 µg/ml	**NA**

Repeatability

Implementing the procedure mentioned under the Method Validation.Six injections were performed on a mixture of Ranolazine and Dronedarone at a concentration of 100 µg/ml. The % RSD was determined to be less than 2%, as seen in (**Table3**).

Table 3: Repeatability data of ranolazine and dronedarone

Sr. No.	Ranolazine; 240 nm	Dronedarone; 280 nm
	Peak Area; Conc. 100 ppm	**Peak Area; Conc. 100 ppm**
01	1051470	2602798
02	1079344	2618176
03	1079682	2647769
04	1064561	2653480
05	1065212	2706691
06	1033731	2730306
Mean	**1062333.34**	**2659870**
STD. DEV.	**17548.18**	**49671.53**
RSD (%)	**1.65**	**1.87**

Number of experiments n= 6

Intraday precision of ranolazine and dronedarone

Implementing the procedure mentioned under the Method Validation. On the same day, three replicates of a combination consisting of 100 ppm each of Ranolazine and Dronedarone were tested and analysed (intra-day precision) [17, 18]. As a result, the RSD was originate within a range of 2% for both Ranolazine and Dronedarone (**Table 4**).

Table 4: Intraday precision data of ranolazine and dronedarone

	Ranolazine				Dronedarone			
Sr. No.	**Conc. (ppm)**	**Area**	**Mean ± SD**	**%RSD**	**Conc. (ppm)**	**Area**	**Mean ± SD**	**%RSD**
	100	1051470			100	2602798		
1	100	1079342	16190.94875	1.51	100	2618176	22856.87123	0.87
	100	1079682			100	2647769		
	100	1064561			100	2653480		
2	100	1065212	17989.42664	1.71	100	2706691	39351.64762	1.46
	100	1033733			100	2730306		
	100	1066441			100	2702585		
3	100	1053525	13562.76457	1.29	100	2679642	11480.01055	0.43
	100	1047108			100	2690348		
			Range of % RSD	**1.29-1.71**			Range of % RSD	**0.43-1.46**

Values are expressed as mean±SD, Number of experiments n= 3

Interday (intermediate) precision of ranolazine and dronedarone

Implementing the procedure mentioned under the method validation, a homogeneous mixture of Ranolazine and Dronedarone, with three sets of three identical concentrations. A concentration of 100 ppm was tested and analysed over three days (interday/intermediate precision) [19]. The computed RSD is under 2%, hence the data is reliable (**Table 5**).

Table 5: Interday (intermediate) precision data of ranolazine and dronedarone

	Ranolazine				Dronedarone			
Sr. No.	**Conc. (ppm)**	**Area**	**Mean ± SD**	**% RSD**	**Conc. (ppm)**	**Area**	**Mean ± SD**	**% RSD**
DAY 1	100	1051470			100	29602798		
	100	1079342	16191.24266	1.51	100	29618176	22856.87123	0.08
	100	1079683			100	29647769		
DAY 2	100	1050015			100	28693901		
	100	1023901	16175.03264	1.57	100	28711338	19551.84355	0.07
	100	1020422			100	28732931		
DAY 3	100	1022651			100	29781638		
	100	1006823	9648.623183	0.95	100	29794861	571157.4838	1.94
	100	1005177			100	28799042		
			Range of % RSD	**0.95-1.51**			Range of % RSD	**0.07-1.94**

Values are expressed as mean±SD, Number of experiments n= 3

The aforementioned concentrations were measured and analysed over three consecutive days using the protocol described in the experimental section. The calculated % RSD values are presented in **Table 5**. The accuracy of the HPLC method is defined as the degree to which a set of measurements taken from independent samples of the same homogenous population yield the same results under the same experimental conditions. Across the studied range of 100 µg/ml for both Ranolazine and Dronedarone, this approach has shown to be exceptionally exact, with intra- and inter-day variations in the range of 0.1 µg/ml or less observed in precision tests. In addition, there was a positive correlation between the peak area of the samples analysed and the concentrations of interest, with % RSDs of 2%. **Table 4** displays RSDs in the range of 1.29-1.71 % for Ranolazine and 0.43-1.46 % for Dronedarone from intra-day studies, while **Table 5** displays RSDs in the range of 0.95-1.51 % for Ranolazine and 0.07-1.94% for

Dronedarone from inter-day studies, demonstrating acceptable precision with minimal variations in the proposed method.

Linearity and range of ranolazine and dronedarone

Every HPLC technique is considered linear if it yields results proportionate to the concentration of the examined analyte within the range chosen [20]. Thus, for both Ranolazine and Dronedarone, extraordinarily high linearity was seen between the concentration and peak area over the range of 6.25-100 µg/ml, with linear regression observed for Ranolazine and Dronedarone being; $y = 8817x + 19806$; and $y = 29255x-3494.8$, respectively (**Fig. 3**). Furthermore, the r^2 values for both samples were very close to 0.999, indicating a high degree of linearity (**Table 6**).

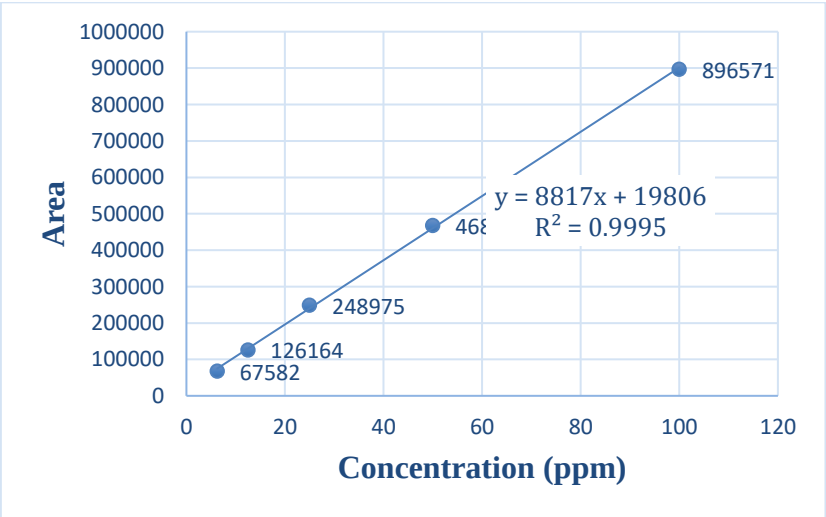
Limit of detection and quantification of ranolazine and dronedarone

Both the LOD and LOQ were calculated using the standard deviation of the answer and the slope of the regression line as inputs [21]. Comparing Ranolazine and Dronedarone, the lower limits of detection (LOD) and lower limits of quantification (LOQ) were found to be 4.67 and 14.17 µg/ml and 21.56 and 65.35 µg/ml, respectively. At the lowest feasible concentration of simultaneously investigating selected medicines from the combination, it indicated the method's stronger detection capabilities.

Table 6: Linearity data of ranolazine and dronedarone

	Ranolazine			Dronedarone		
Sr. No.	**Conc. (µg/ml)**	**Area**	**Average (Mean)**	**Conc. (µg/ml)**	**Area**	**Average (Mean)**
1	100 ppm	896571	896571	100 ppm	2939385	2939385
2	50 ppm	468025	468025	50 ppm	1416389	1416389
3	25 ppm	248975	248975	25 ppm	735205	735205
4	12.5 ppm	126164	126164	12.5 ppm	379943	379943
5	6.25 ppm	67582	67582	6.25 ppm	179796	179796
6	Regression Equation		*y = 8817x + 19806*	*y = 29255x + 3494.8*		
7	Correlation coefficient (r^2)		0.9995	0.9998		
8	Std. Error of intercept		41702.67714	19576.57037		
9	Std. Dev. of intercept		93250.02093	43774.54211		
10	LOQ		18.61 µg/ml	6.69 µg/ml		
11	LOD		6.14 µg/ml	2.00 µg/ml		

Number of experiments n= 5



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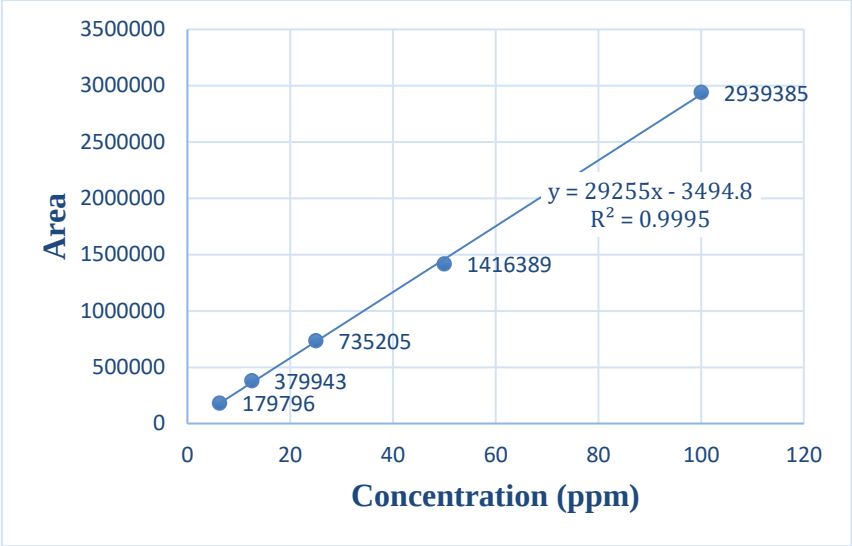

(b)

Fig. 3: Calibration curve of (a) ranolazine and (b) dronedarone

Robustness of the chromatographic method

By systematically varying the flow rate (1.0± 0.2 ml/min), organic modifier (83±2% mL), and temperature (32±2 nm), the method's resilience was established. Increases in flow rate resulted in shorter $t_R$values for Ranolazine and Dronedarone of 1.51 and 4.195 min, respectively (**Fig. 4**), while decreases in flow rate resulted in longer $t_R$values of 2.12 and 5.98 min for the same medicines.Furthermore, when the CH_3OH concentration was increased by +2%, the routine t_R values of Ranolazine and Dronedarone were changed to 1.82 and 5.42 mins (**Fig. 4**),similarly, the alteration of MeOH -2% the t_R values of both drugs remained unchanged to 2. In addition, with alteration in temperature by ±2 ˚C (30˚C and 34˚C) there have been no noteworthy shifts in retention time for any medication [22].

Thus, affecting the flow rate alters the elution time of both Ranolazine and Dronedarone where increasing the flow rate enhances the decrease in the t_R value and *vice versa*. The retention pattern of both medications has been relatively stable regardless of the concentration and temperature of the organic modifier. Nevertheless, except theoretical plates, other separation parameters such as k' values, resolution (R_s), peak tailing and peak fronting (*T*) were essentially unaltered, indicating that the suggested technique met or exceeded all USP and ICH minimum standards (**Table 7**) [16].

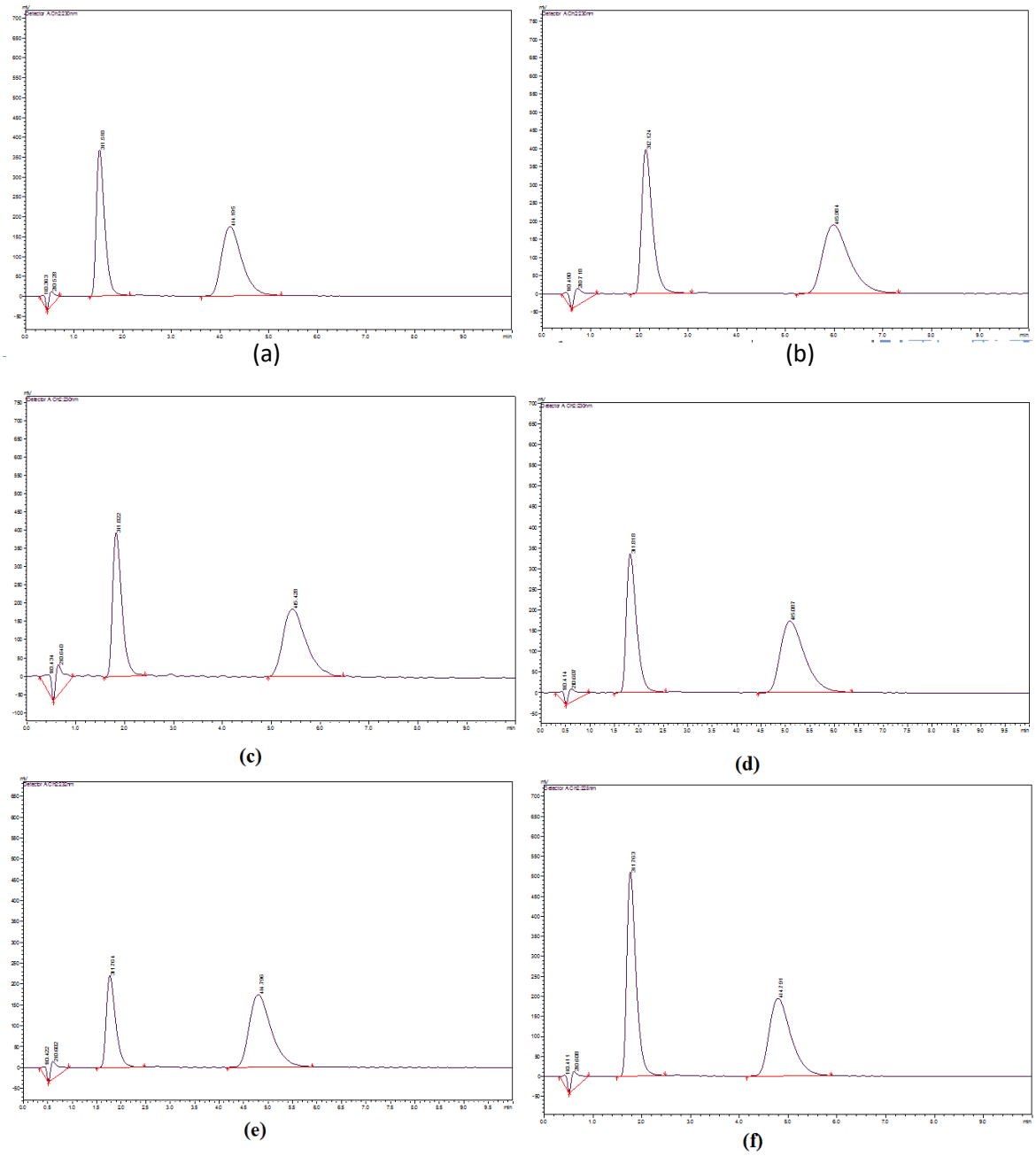

Fig.4: (a) Robustness studies of ranolazine and dronedarone at flow rate (1.4 ml/min),

(b) Robustness studies of ranolazine and dronedarone at flow rate (1 ml/min)

(c) Robustness studies of ranolazine and dronedarone with a concentration of organic modifier methanol 82 ml,

(d) Robustness studies of ranolazine and dronedarone witha concentration of organic modifier methanol 78 ml,

(e) Robustness studies of ranolazine and dronedarone at a temperature of 34˚C,

(f) Robustness studies of ranolazine and dronedarone at a temperature of 30˚C

Table 7: Robustness data of ranolazine and dronedarone

Sr. No.	Flow rate (-0.2 ml/min)	Flow rate (+0.2 ml/min)	Organic Modifier (-2 ml)	Organic Modifier (+2 ml)	Temper-ature (-2^0C)	Tempe-rature ($+2^0$C)
Robustness data of ranolazine						
Resolution	**----**	**----**	**----**	**----**	**----**	**----**
Tailing factor	1.61	1.57	1.61	1.6	1.5	1.6
Capacity factor	3.33	3.18	3.39	3.2	3.33	3.18
Theoretical Plates	454	370	370	441	433	410
Robustness data of dronedarone						
Resolution	5.58	5.02	6.27	6.27	6.32	5.21
Tailing factor	1.46	1.45	1.34	1.52	1.45	1.46
Capacity factor	11.21	10.57	11.29	11.51	10.79	10.38
Theoretical Plates	592	499	515	601	547	552

Number of experiments n= 3

Forced degradation studies

Degradation studies of Ranolazine and Dronedarone under the impact of acid-base strength, peroxide and temperature environment were found by the use of SCX chromatography as a forced degradation technique. It was found that the compounds were stable after being treated with 0.1N HCl since no degradation products showed up in the chromatogram. (**Fig. 5**) (**Table 8** to **12**). The treatment with 3% H_2O_2-produced oxidative stress has not made any significant changes in t_R values since no fragments of degradants have appeared. Similarly, there was no change in the retention of Ranolazine or the production of new degradation products when the sample was subjected to thermal stress at 50°C (**Table 12**) [12, 23].

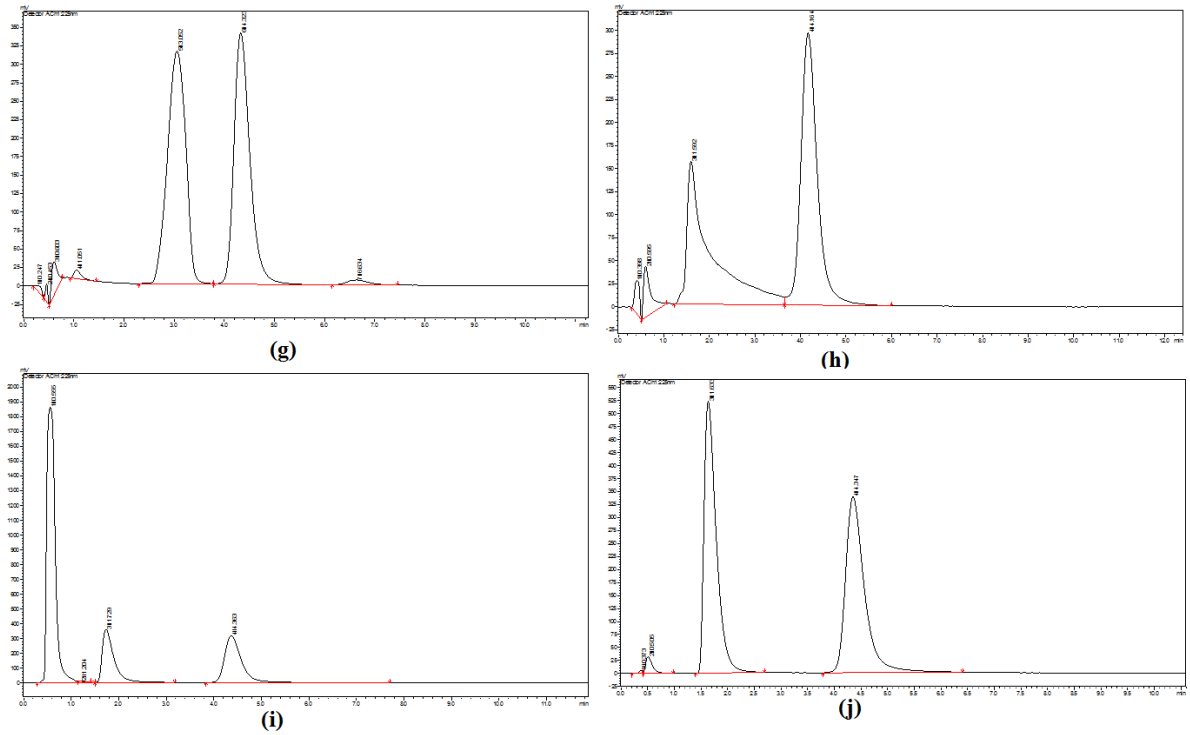

Fig. 5. (g) 0.1N HCl induced stress effect on ranolazine and dronedarone,

(h) 0.1N NaOH induced stress effect on ranolazine and dronedarone,

(i) 3% H_2O_2 induced stress effect on ranolazine and dronedarone,

(j) Thermal (50˚C) induced stress effect on ranolazine and dronedarone.

Table 8: Degradation data of ranolazine and dronedarone using 0.1N HCl

Peak#	Ret. Time	Area	Area%	T. Plate#	Resolution	k'	Tailing Factor	Separation
Impurity	1.051	624418	3.0021	25.366	--	0	2.106	0
Ranolazine	3.052	6752341	50.4809	180.542	5.132	1.705	1.777	0
Dronedarone	4.323	5999260	44.8509	368.158	2.987	4.675	1.575	2.742
Impurity	6.634	731124	3.6682	425.366	4.231	7.712	1.606	3.891

Number of experiments n= 3

Table 9: Degradation data of ranolazine and dronedarone using 0.1N NaOH

Peak#	Ret. Time	Area	Area%	T. Plate#	Resolution	k'	Tailing Factor	Separation
1	0.592	560667	4.5693	77.043	--	0	0.811	0
Ranolazine	1.592	6094954	49.6725	171.094	1.772	0.926	1.713	0
Dronedarone	4.164	5614664	45.7582	373.285	1.436	2.81	1.598	3.036

Number of experiments n=3

Table 10: Degradation data of ranolazine and dronedarone using 3% H_2O_2

Peak#	Ret. Time	Area	Area%	T. Plate#	Resolution	k'	Tailing Factor	Separation
1	0.555	1447	0.0067	29.365	--	0	1.859	0
2	1.204	447	0.0019	39.365	--	0	1.859	0
Ranolazine	0.899	10442633	48.1352	137.111	2.108	2.72	1.987	0
Dronedarone	1.915	11250282	51.8581	308.746	4.736	6.925	1.681	2.546

Number of experiments n=3

Table 11: Degradation data of ranolazine and dronedarone using thermal (50˚C)

Peak#	Ret. Time	Area	Area%	T. Plate#	Resolution	k'	Tailing Factor	Separation
1	0.505	207568	1.6273	134.857	--	0	1.095	0
Ranolazine	1.633	6713135	52.6283	165.336	2.082	1.009	1.554	0
Dronedarone	4.347	5835059	45.7445	311.004	4.864	3.301	1.944	3.271

Number of experiments n=3

Table 12: Force degradation studies of ranolazine and dronedarone

Conditions	Ranolazine		Dronedarone	
	No. of degradants (fragments)	% degradation	No. of degradants (fragments)	% degradation
Acid (0.1N/M HCl) + 60˚C + 12 Hrs.	0 Fragment	0 %	0 Fragments	0%
Base (0.1N/M NaOH) + 60˚C + 12 Hrs.	0 Fragments	0 %	0 Fragments	0%
Thermal (60˚C) + 12 Hrs.	0 Fragment	0 %	0 Fragments	0%
Oxidation (3-6% H_2O_2) + Room Temp.	0 Fragments	0%	0 Fragments	0%

CONCLUSION

The suggested method for the estimation of Ranolazine and Dronedarone using Ion Exchange Chromatography was assessed for linearity, precision, accuracy and system suitability; it was found useful for the estimation of these drugs. With a correlation coefficient correlation value of 0.999, it was found accurate and linear across the concentration range examined (6.25 to 100 µg/ml). Also by adopting this method, it was observed that the simultaneous estimation of Ranolazine and Dronedarone improved UV sensitivity at 240 and 280 nm by increasing

resolution (R) and capacity factor (CF) (k). Splitting took 8 minutes. Also increased flow rate to 1.2 ml/min improved resolution and peak symmetry. It is clear from the results obtained that the suggested method may be used to determine Ranolazine and Dronedarone with high sensitivity without causing any interference. As a result, the proposed method is selective and useful for the quantification of Ranolazine and Dronedarone.

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AUTHOR CONTRIBUTIONS

All authors made substantial contributions to the conception and design, acquisition of data, or analysis and interpretation of data; took part in drafting the article or revising it critically for important intellectual content; agreed to submit to the current journal; gave final approval of the version to be published; and agree to be accountable for all aspects of the work.

CONFLICTS OF INTEREST

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

ETHICAL APPROVALS

Not applicable.

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