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SOLUBILITY ENHANCEMENT OF RANOLAZINE BY HYDROTROPIC METHOD

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ABSTRACT

The present work was focused at development of a novel and validated technique for solubility enhancement by principle of hydrotropic method for low soluble anti anginal drug ranolazine in pure form. It was estimated using UV spectrophotometry at 268 nm and hydrotropic agent urea (6 M) has no interference with drug estimation. The % Recovery for the ranolazine drug at the 268 nm was found to be 99-100.20 %. Linearity for ranolazine was found to be in range of 10-100 mg/ml (Y = 0.004x +0.066, R^2 =0.999). Limit of detection was found to be 0.4760 mg/ml and Limit of quantification was found to be 1.4425 mg/ml. The results showed that there was an increase in the solubility of ranolazine with hydrotropic method compared to pure drug in distilled water. There was 8.390-fold enhancement in aqueous solubility of ranolazine with urea as a hydrotropic agent. In order to elucidate the interaction, a UV spectrophotometric method was developed is simple, economical, accurate and validated by using urea 6 M as a hydrotropic agent.

Keywords *– Ranolazine, Hydrotopic method, Solubility enhancement method, UV spectrophotometry.*

1. INTRODUCTION

Ranolazine is an anti-anginal medication. It works by improving blood flow to help the heart work more efficiently. Ranolazine is used to treat chronic angina (chest pain). Ranolazine is not for use during an acute (emergency) attack of angina.

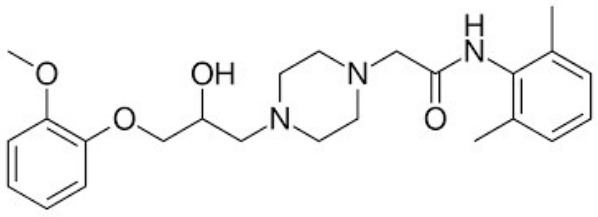

Fig. 1: Chemical structure of Ranolazine

Structurally, it is N-(2,6-dimethylphenyl)-2-[4-[2-hydroxy-3-(2-methoxyphenoxy) propyl] piperazin-1-yl] acetamide. Its molecular formula is $C_{24}H_{33}N_3O_4$ and molecular weight is 427.545 g/mol. Ranolazine is soluble in dichloromethane and methanol; sparingly

soluble in tetrahydrofuran, ethanol, acetonitrile, and acetone; slightly soluble in ethyl acetate, isopropanol, toluene, and ethyl ether; and very slightly soluble in water [1-3].

Hydrotropic is a solubilization process where addition of a large amount of second solute exerts an increase in the aqueous solubility of another solute. The other solute can be a poorly soluble drug. Hydrotropes may be cationic, anionic or a neutral molecule, and possesses a hydrophobic as well as a hydrophilic group. Finding the right hydrotropic agent for a poorly soluble drug requires screening of a large number of hydrotropic agents. However, significant solubility enhancement of drug can be easily achieved by selecting correct hydrotropic agent. Hydrotropic solubilization technique is a promising approach with great potential for poorly soluble drugs. In this method, chemical modification of the drug, use of organic solvents and preparation of emulsion systems is not required [4-10].

2. MATERIALS AND METHODS

2.1 Reagents

Ranolazine (Gift sample from Aarti Industries Limited - Custom Synthetic Division)**.** Sodium acetate (Thomas Baker)**.** All chemicals used were of analytical grade Urea (OZONE).

2.2 Instruments

Spectrophotometric was carried out by using UV-Visible spectrophotometer having two matched quartz cell with 1 cm light path, Model: Shimadzu-1800, Software: -UV probe, version Electronic analytical balance (REPTECH) Ultrasonicator (LOBA Life) Mechanical flask shaker Centrifuge (Remi-electro technique Ltd.).

2.3 Method

2.3.1 Preparation of Drug Solution

To make final concentration up to 100 µg/ml dissolve 10 mg drug in 100 ml distilled water. The stock solution further diluted with suitable distilled water to make concentration of 10µg/ml.

2.3.2 Preparation of Sodium Acetated and Urea Solution

To prepare 2 M sodium acetate solution 27 g sodium acetate was added in 100ml distilled water. Then 12.012 g Urea added in 100 ml distilled water for 2 M Urea solution.

2.3.3 Preparation of 2 M, 4 M, 6 M, 8 M Urea Solutions

To prepare 2 M Urea solution, 12.012 g Urea was dissolved in 100 ml distilled water and stirred well to make solution. Then accordingly 24,024 g Urea for 4 M solution, 36.036 g Urea for 6 M solution and 48.04 g Urea for 8 M solution were prepared. The 2 M, 4 M, 6 M and 8 M Urea solution was scanned in UV range 200-400 nm.

2.3.4 Hydrotropic Solubilization Method

Preliminary Solubility Study of Drug

Solubility of Ranolazine was determined at 28±1°. 1 g drug was added in a 100 ml 2 M Urea solution. The solution was shaken mechanically for 12 hr in mechanical shaker. These solutions were allowed to equilibrate for the next 24 h. Then centrifuge for 5 m at (2000 rpm). Then filter the solution through Whatman filter paper. The filtrates were diluted suitably and take absorbance against corresponding blank.

Preparation of Standard 6 M Urea Solution

In hydrotropic solubilization method, 10 mg of pure Ranolazine was dissolve in 50 ml 6 M Urea solution and the solution stirred for 15-20 m and the final volume make up to 100 ml with distilled water. The solution was filtered through Whatman filter paper and diluted with distilled water to prepare 100 µg/ml working concentration of Ranolazine.

Preparation of Standard Working Solution

a) Procedure for preparation of Ranolazine Standard stock solution (1000 µg/ml) 100 mg of Ranolazine was weighed and transferred to a 100 ml volumetric flask and add 50 ml 6 M Urea and finally volume made up to mark with distilled water.
b) Procedure for preparation of Ranolazine Working stock solution (100 µg/ml) Aliquot of 10 ml from above solution was pipette out into 100 ml of volumetric flask and volume made up to mark with distilled water.

2.4 Method Validation [11-12]

2.4.1 Linearity

The solution were prepared by pipetting 1, 2, 3, 4, 5, 6, 7, 8, 9 and 10 ml from working standard stock solution in to 10 ml volumetric flask and the volume was adjusted to mark with distilled water to produce 10-100 µg/ml respectively. The absorbance of solution was measured at 268 nm. Calibration curve were generated by taking the response vs. concentration.

2.4.2 Accuracy

The accuracy of the method was determined by calculating recovery of Ranolazine by the standard addition method. Reference standard solution of each drug was added to samples at three different concentration levels (80%, 100% and 120%). At each level sample were prepared in triplicate and the mean percentage recoveries and %RSD value were calculated.

2.4.3 Precision

Repeatability

Aliquots of 7 ml of working standard solution of Ranolazine (100 µg/ml) was transferred to 10 ml volumetric flask and volume was adjusted to distilled water to get concentration of 70 µg/ml. the absorbance of solution was measured spectrophotometry six times and %RSD was calculated.

Intraday and interday

Aliquots of 6, 7and 8 ml of working standard solution of Ranplazine(100 µg/ml) was transferred to 10 ml volumetric flask and volume was adjusted to distilled water to get concentration of 60, 70, and 80 µg/ml. The absorbance of solution was measured in spectrophotometry three times and %RSD was calculated. For intraday, the analysis was carried out at different intervals on the same day and for interday, the analysis was carried on different days.

2.4.4 LOD and LOQ

Limit of detection (LOD)

The LOD is estimated from the set of 3 calibration curves used to determine method linearity. The LOD may be calculated as,

LOD=3.3*SD/Slope

Where,

SD=the standard deviation

Y=intercept of 3 calibration curves

Slope=the mean of slope of the 3 calibration curves.

Limit of Quantitation (LOQ)

The LOQ is estimated from the sets of 3 calibration curves used to determine method linearity. The LOQ may be calculated as,

LOQ=10*SD/Slope

Where,

SD=the standard deviation

Y=intercept of 3 calibration curves

Slope=the mean of slope of the 3-calibration curve.

2.4.5 Robustness

Aliquots of 7 ml of working standard solution of Ranolazine (100 µg/ml) was transferred to 10 ml Volumetric flask and volume were adjusted to distilled water to get concentration of 70 µg/ml. the absorbance of solution was measured spectrophotometry in three different wavelengths 266 nm, 268 nm and 270 nm in three times the SD and % RSD was calculated.

3. RESULTS AND DISCUSSION

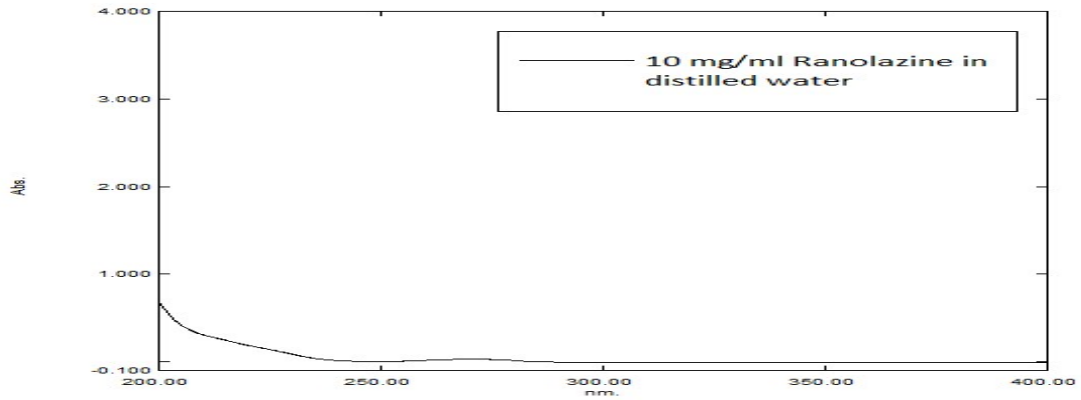

Fig. 2: 10 mg/ml Ranolazine in distilled water

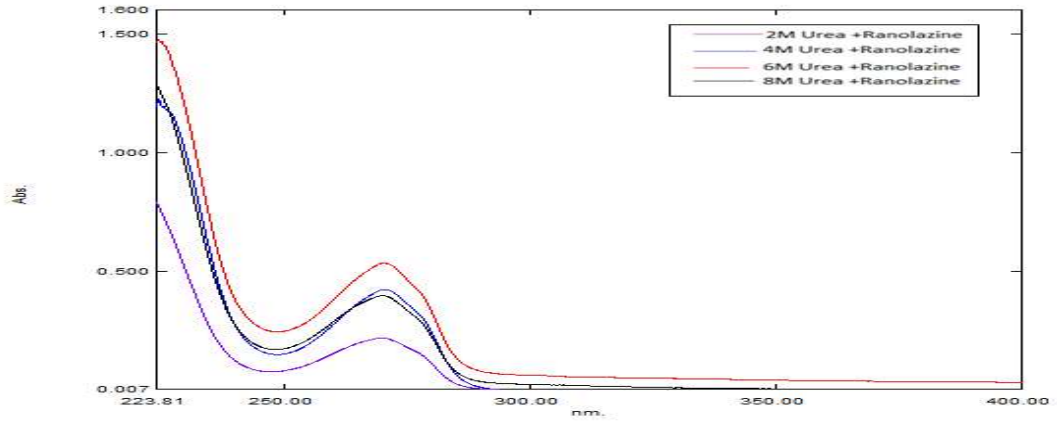

Fig. 3: Ranolazine drug with 2 M, 4 M, 6 M, and 8 M urea

Table-1: Linearity study of Ranolazine (n=3)

Sr. No.	Conc. (µg/ml)	Absorbance at 268 nm ± SD
1	10	0.1155±0.000451
2	20	0.1513±0.000306
3	30	0.1914±0.000404
4	40	0.2394±0.000351
5	50	0.2799±0.000306
6	60	0.3208±0.0003
7	70	0.3697±0.000764
8	80	0.4191±0.000252
9	90	0.4558±0.000351
10	100	0.4973±0.000351

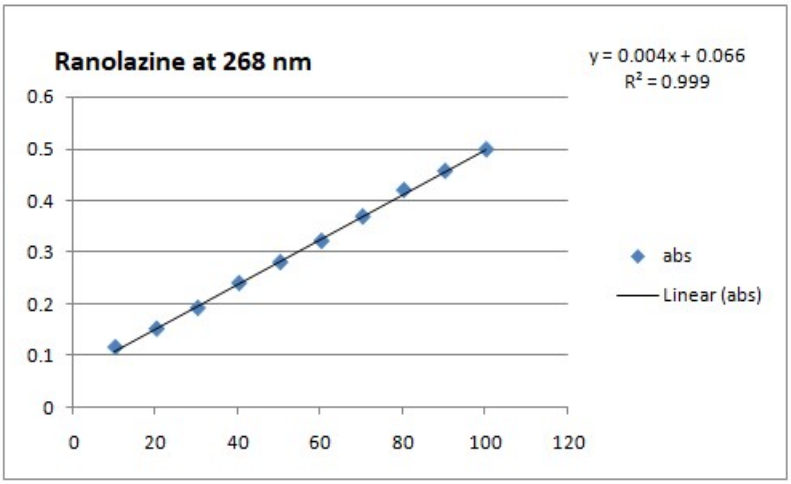

Fig. 4: Calibration curve of Ranolazine

Table – 2: Determination of Accuracy data of Ranolazine at 268 nm (n=3)

Level	Amount of drug taken (µg/ml)	Amount of standerd drug added (µg/ml)	Total amt. (µg/ml)	Absorbance	Recovery	% Recovery
80%	70	56	126	0.5695	125.69	99.91
100%	70	70	140	0.6268	140.21	100.14
120%	70	84	154	0.6832	154.32	100.20

Table – 3: Intraday Precision data of Ranolazine at 268 nm

Concentration (µg/ml)	At 268 nm		
	Absorbance	Mean ± SD (n=3)	%RSD
60	0.3208 0.3211 0.3205	0.3208±0.000301	0.093516
70	0.3682 0.3697 0.3692	0.3690±0.000764	0.206693
80	0.4191 0.4193 0.4188	0.4190±0.000252	0.060053

Table – 4: Interday Precision data of Ranolazine at 268 nm

Concentration (µg/ml)	At 268 nm		
	Absorbance	Mean ± SD (n=3)	%RSD
60	0.3309 0.3313 0.3315	0.331233±0.00306	0.092233
70	0.3778 0.3851 0.3855	0.3828±0.004335	1.132378
80	0.4292 0.4297 0.4310	0.4310±0.000929	0.21610

Table - 5: LOD and LOQ data of Ranolazine at 268 nm

Sr. No.	Slope	Intercept
1	0.004	0.066
2	0.004	0.065
3	0.004	0.066
Mean	0.004	0.065
SD		0.000577
LOD	0.4760 µg/ml	
LOQ	1.4425 µg/ml	

Table – 6: Robustness data of Ranolazine at 268 nm

Sr. No	Wavelength (268 ± 2 nm)	Absorbance	Mean	SD	RSD
1	266	0.3598 0.3597 0.3594	0.3596	0.000208	0.05788
2	268	0.3697 0.3692 0.3682	0.36903	0.000764	0.20696
3	270	0.3591 0.3589 0.3592	0.3590	0.000153	0.04252

4. CONCLUSION

In this Hydrotropic method were used for the poorly water-soluble drug Ranolazine using solubilizing agent urea; result from studies were found satisfactory. It was conducted the solubility of Ranolazine greatly enhance by synergistic effect of hydrotropic agents. Thus, the research work overcome the problem of poorly water-soluble drug and present methodology is a viable and cost-effective means to increase the solubility of poorly water-soluble drugs. Ranolazine, a poorly water-soluble drug, having water solubility 0.044 mg/ml. The solubility of Ranolazine was increased by using urea as a solubilize. The develop method is simple, precise, economic and rapid can employ in routine analysis of estimation of the Ranolazine drug. And also, this method is cost-effective, safe in bulk.

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