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Novel UV-Spectrophotometer Methods for Quantitative Estimation of Reloxifene Hydrochloride using Hydrotrophy Solubilization Technique

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ABSTRACT
The present study was aimed to develop a hydrotrophy technique to increase the solubility of poorly water soluble drug. This technique is used to estimate the amount of Reloxifene Hydrochloride in bulk drug and tablets by spectrophotometric method by using tri Sodium benzoate as hydrotropic agent. Beer's law was obeyed in the concentration range of 2-20µg/ml and showed maximum absorbance at 286nm. The solubility of Reloxifene Hydrochloride in distilled water was found to be very less and then by adding hydrotropic agent solubility was increased as compared with distilled water. The analysis of tablets indicated good correlation between estimated and label claim. The LOD and LOQ of Reloxifene Hydrochloridewas found to be 3.41µg/ml and 10.35µg/ml respectively indicated good sensitivity of proposed method. The percentage recovery was found to be 99.18%-99.607%. The proposed method is new, simple, accurate,non-toxic and precise method that can be successfully employed for estimation of drugs in routine analysis of tablets.

Key Words: *Hydrotrophy technique, Reloxifene Hydrochloride, Sodium benzoate, solubilisation, UV spectrophotometry.*

INTRODUCTION

Increasing the aqueous solubility of insoluble and slightly soluble drugs is major importance. This is because mostof the newly developed drugs are highly lipophilic in nature and its analysis was mainly carried out using organicsolvents like methanol, chloroform, ethanol, benzene, acetone, toluene, carbon tetrachloride, diethyl ether andacetonitrile. Most of these organic solvents are toxic, volatile and costlier. This may cause inaccuracy in analytical
methods. Various techniques have been employed by the researchers to improve the aqueous solubility of lipophilicdrugs and hydrotropy is one among them [1]. Hydrotropy can be considered to be potentially and industriallyattractive technique since the observed increase in solubility is much higher than that affected by other solubilisation method. Several works have been reported on use of hydrotropic solvents in estimation of various poorly water
soluble drugs using some of the hydrotropic agents like sodium benzoate, sodium salicylate, niacinamide, sodiumascorbate, and urea [2-5]. But it was observed that hydrotropy is another type of cosolvency, which is utilized toimprove the aqueous solubility of poorly water soluble drugs. Based on this approach to increase solubility oflipophilic model drug Reloxifene Hydrochloride. These hydrotropic agents do not cause any toxicity and non-volatile in nature.In the present work the total concentration of hydrotropic agent was kept constant 2Molar concentration.

Raloxifene hydrochloride (RLX) is the chemical designation is methanone, [6-hydroxy-2-(4-hydroxyphenyl) benzo [b] thien-3-yl]-[4-[2-(l-piperidinyl) ethoxy] phenyl]-, hydrochloride. Raloxifene hydrochloride1 is an anti osteoporotic drug, first selective estrogen receptor modulator (SERM) for the prevention and treatment of osteoporosis in postmenopausal women. It affects the cycle of bone formation and breakdown in the body and reduces loss of bone tissue. It produces estrogen-like effects on bone, reducing re sorption of bone and increasing bone mineral density in postmenopausal women. It is a poly hydroxylated non-steroidal benzothiophene compound.

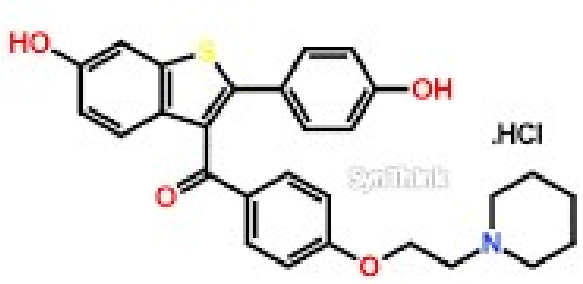

Figure 1: Structure of Raloxifene hydrochloride (RLX)

MATERIALS AND METHODS

Raloxifene hydrochloride (RLX)bulk drug was gift sample from Cipla LTD.,Indore,India.The Raloxifene hydrochloride (RLX) formulation(Tablet) was received from local market.Shimadzu UV/Visiblerecording spectrophotometer(model-UV-1900I) with 1cm matched silica cells was employed. Allother chemicals and solvents used were of analytical grade.

Selection of hydrotropic solubilising additive:

Various hydrotropic solubilising additives like Sodium acetate, Sodium benzoate, Niacinamide, Ibuprofen sodium, N-N Dimethyl Urea, N-N Dimethyl Urea Sodium citrate etc. were tried.The N-N Dimethyl Urea and N-N Dimethyl Urea Sodium citrate on addition to drug solution causes sedimentation of drug. Addition of niacinamide leads to turbidity.
The Sodium benzoate renders complete solubilisation of drug.Hence Sodium benzoate was selected as hydrotropic solubilising additive.The volume of Sodium benzoate added to solubilise Raloxifene hydrochloride (RLX) was optimized to be in the ratio of 4:1.

Preparation of the standard stock and calibration curve

Anaccurately weighed 100mg quantity of Raloxifene hydrochloride (RLX) was transferred in to a 100ml volumetric flask. To this, 100ml of 2M Sodium benzoate solution was added and the flask was shaken for 1 mins to solubilise the drug to get a standard stock solution of 1mg/ml. This stock solution used for further dilutions and by using distilled water as solvent for estimation.
The absorption maxima of Raloxifene hydrochloride(RLX) were found to be 286 nm (Fig.1). Working standard solutions ranging from concentration of 2 to14µg/ml was prepared with 2M Sodium benzoate solution from thestock solution. The absorbance of resulting solutions were measured at wavelength of 286nm against solvent blank and a calibration curve was plotted to get the linearity and regression equation. Fig 2.

Analysis of Raloxifene hydrochloride(RLX) in Tablet using mixed cosolvents

Weigh accurately about 10 tablets powder and take 100mg equivalent quantity of Raloxifene hydrochloride (RLX)and transfer into a 100ml standard flask. And add 100 ml of 2M Sodium benzoate solutionby using ultrasonication. Then pipette out 1ml of solution and make up to 100ml leads to 10µg/ml concentration solution. The absorbance of the resulting solution was measured at 286nm against solvent blank and drug content was calculated.

Validationoftheproposedmethod

The proposed method was validated for the following parameters.[12-15]

Precision

Precision was determined by studying the repeatability and intermediate precision.The standard deviation, coefficient of variance and standard error were calculated for the drug.

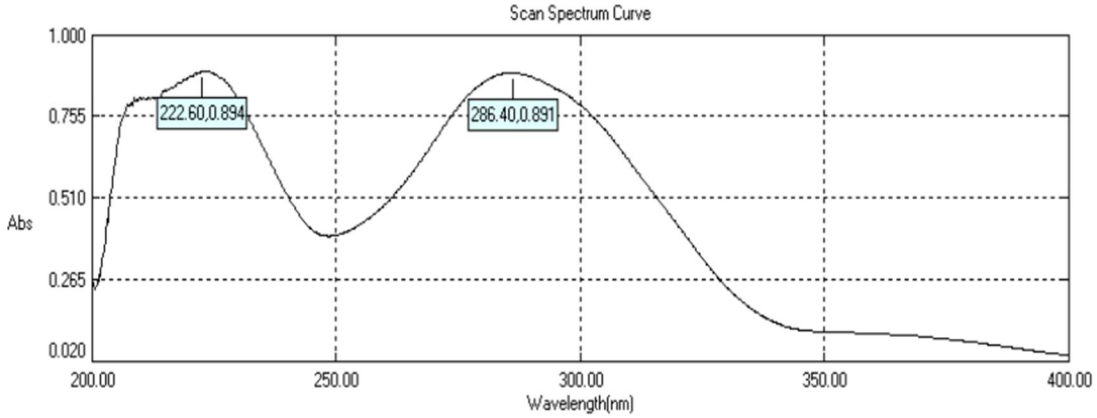

Figure-2

Inter-dayandIntra-dayprecision

The intra-day concentration of the drug was calculated on the same day at an interval of two hour. Whereas the interday concentration of drug was calculated on three different days within the laboratory conditions.

4.1Data table for repeatability of Raloxifene hydrochloride.

S.NO.	Conc. (µg/ml)	Conc. Found	Conc. Found (µg/ml)	Mean MC Value	SD	%RSD
1.	10	9.8639	9.97	9.87096	0.80293	0.164841
2.	10	9.8687	9.98			
3.	10	9.8745	9.98622			
4.	10	9.8854	9.7944			

5.	10	9.8649	9.9764			

The above table shows five replicate date for Raloxifene hydrochloride with Conc.10µg/ml and %RSD was found to be 0.164841.

B**) Intraday Precision**

4.2 Data of Intraday Precision of Raloxifene hydrochloride.

The above result shows the %RSD for precision sets for Raloxifene hydrochloride were 0.134003,

S.NO.	Conc. (µg/ml)	Conc. Found			Mean	SD	%RSD
		Time 1	Time 2	Time 3			
1.	5	5.0441	5.03218	5.02875	5.035032	0.8087142	0.134003
2.	10	10.3799	10.3578	10.3523	10.363388	0.1460471	0.140936
3.	15	15.782	15.6985	15.6985	15.718827	0.5598566	0.380368

0.140936 and 0.380368 for low medium and high concentration level which is less then 2% stated by ICH guidelines.

(c) **Interday Precision**

4.3 Data of interday Precision of Raloxifene hydrochloride

S.NO.	Conc. (µg/ml)	Conc. Found			Mean	SD	%RSD
		Day-1	Day-2	Day-3			
1.	5	4.0387	4.062671	4.995655	4.032355	0.33961	0.562985
2.	10	9.349012	9.394389	9.387611	9.377004	0.2447753	0.23588
3.	15	14.682981	14.898735	14.86453	14.15420	0.1159624	0.782714

The above result shows the %RSD for precision sets for Raloxifene hydrochloride were 0.562985,0.23588 and 0.782714 for low medium and high concentration level which is less then 2% stated by ICH guidelines.

Linearity

Linearity of Raloxifene hydrochloride was found to be 2-14µg/ml.

Limit of detection(LOD) and Limit of Quantitation(LOQ)

5.1 Limit of detection and limit of Quantitation for Raloxifene hydrochloride

S.D of calibration curve	Mean S.D.	Slope	LOD	LOQ
0.33632	0.104948	0.1014	3.41546746	10.3499014
0.14654				
0.90467				
0.176800				
0.155036				

The above table shows the Limit of Detection and limit Quantification data for Raloxifene hydrochloride .the LOD and LOQ were found to be 3.546976 and 10.748386 respectively.

Accuracy

Accuracy is the percentage of analytes recovered by assay from known added amount. Analysis was performed at 80%, 100%, 120% levels.

Molar Absorptivity

This is the important factor for determining the absorptive property of a drug in1mole concentration. And this value can be useful in determining the absorbance of drug in molar concentrations. This for identifying the shifts of the maximum absorbance of the drug during the method development.

RESULTS AND DISCUSSION

The solubility studies showed that aqueous solubility of of Raloxifene hydrochloride was increased by adding Sodium benzoate as hydrotropic solubilising agent.The Beer-Lambert's concentration range for of Raloxifene hydrochloridewasbetween2-10µg/ml. To check drug stability and precipitation of drug in solvent, a part of solution were kept in room temperature for 48 hours.The results revealed that estimation of Raloxifene hydrochloride can be done without substantial effect on drug stabilityas no precipitation was observed. From this study it is obvious that there was no interference of Sodium benzoate in estimation of of Raloxifene hydrochloride at the wavelength of 286nm.

Table1: Method Validation Parameters of Raloxifene hydrochloride

Parameters	Observed values
λmax (nm)	286 nm
Beer's range (µg/ml)	2-14 µg/ml
Correlation Coefficient (r^2)	0.997
Regression equation	Y=0.0757x+0.0067
Intercept (a)	0.0067
Slope (b)	0.0757
LOD	0.580 µg/ml
LOQ	1.763 µg/ml

Table-2:Recovery studies (accuracy parameter) of Raloxifene hydrochloride

S.NO.	Con. (µg/ ml)	Con. before addition (µg/ml)	Con. of std add (µg/ml)	Con. after addition (µg/ml)	% recovery	Mean	SD	% RSD
1.	5	4.945	8	12.69	99.33	99.99	1.449908	1.44995
2.	5	4.852	8	13.70	100.66			
3.	5	4.562	8	12.71	98.0			
4.	5	4.692	10	10.26	100.26	100.83	1.871265	1.869707
5.	5	4.963	10	14.32	98.13			
6.	5	4.521	10	14.69	99.33			
7.	5	4.321	12	16.96	98.88	99.33	0.591523	0.595513
8.	5	5.241	12	16.04	100.0			
9.	5	5.962	12	16.92	99.11			

Table-3: Analysis of tablet formulations of Raloxifene hydrochloride

Drug	Labelclaimmg /Tab	Amountfound	%Purity
Raloxifene hydrochloride	60	98.87±0.218	99.53%w/w

The estimated label claim in the 2M Sodium benzoate Solution was found to be 98.87 ± 0.218 indicating good correlation between estimated and those claimed by the manufacturers. The results of percent label claim were shown in Table

2.The recovery studies showed proposed method is accurate and reproducible. The results of recovery

study revealed that any small change in the drug concentration in the solution could be accurately determined by the proposed method. Accuracy ,reproducibility and precision of the proposed methods were further confirmed by percent recovery values, which were close to 100 with low values of standard deviationas shown in Table 3. Repeatability results indicated the precision under the same operating conditions over a short interval time and inter- assay precision. Intermediate precision study expresses with in laboratory variation in different days. In both intra and inter-day precision study for the method co-efficient of variation was not more than 1.0% indicates good intermediate precision. The low values of LOD and LOQ, 0.054 and 0.169 for Raloxifene hydrochloride indicates good sensitivity of proposed method. (Table 1).

CONCLUSION

This current investigation is intended to use hydrotrophy technique to develop UV specrophotometric method to determine the assay of Raloxifene hydrochloride.The method was validated, for both bulk and formulations. This method involves direct analys is without any extraction steps, thus it is performed faster, simple and easier. And this method is shown accurate and précised results. By these results this method found to be rapid, simple, accurate, economic method for analysis and quality determination.

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