Research Article

Stability indicating RP-HPLC Method for Simultaneous Estimation of Domperidone and Cinnarizine in Bulk and Pharmaceuticeutical Dosage Form

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ABSTRACT

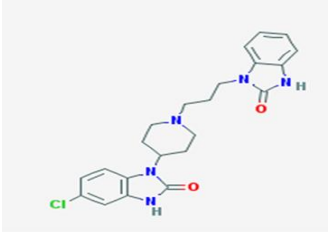
The aim of this study is to a simple, precise, accurate and economic stability-indicating RP-HPLC assay method was developed and validated for simultaneous estimation of Domperidone and Cinnarizine bulk drugs and commercial tablets. The method has rapid shown adequate separation of Domperidone and Cinnarizine from their degradation products. Separation was achieved on a column at wavelength of Luna C_{18}(250x4.6 mm,5µ) 226nm, using a mobile phase Orthophosphoric acid and acetonitrile (70:30) in an isocratic elution mode at a flow rate of 1.0 ml/min. The retention time for Domperidone and Cinnarizine were found to be 2.52min and 5.18min respectively. The above drug combinations were subjected to acid, base, neutral hydrolysis, thermal and photolytic stress conditions. Quantitation was achieved with PDA detection at 226 nm based on peak area with linear calibration curve at concentration ranges for Domperidone is 0-5.5µg/ml(0.9994) and for Cinnarizine is 0-36µg/ml(0.9992). The LOD's were 0.4625µg/ml and 0.615µg/ml for Domperidone and Cinnarizine respectively. The LOQ's were found to be 0.925µg/ml for Domperidone and 0.1.23µg/ml for Cinnarizine. The method was found to be specific and stability indicating as no interfering peaks of degrades and excipients were observed. The proposed method is hence suitable for application in quality-control laboratories for quantitative analysis of both the drugs individually and in combination dosage forms, since it is simple and rapid with good accuracy and precision.

Keywords: Forced degradation studies, Domperidone and Cinnarizine RP-HPLC, Stability indicating assay.

INTRODUCTION

Domperidone facilitates gastric emptying and decreases small bowel transit time by increasing esophageal and gastric peristalsis and by lowering esophageal sphincter pressure. Domperidone also has the antiemetic activity and some of the antiemetic properties of Domperidone are related to its dopamine receptor blocking activity at both the chemoreceptor trigger zone and at the gastric level. It has strong affinities for the D_2 and D_3 dopamine receptors, which are found in the chemoreceptor trigger zone.

Cinnarizine[2,4] (Figure:1.b) is chemically 1-(Diphenyl methyl)-4-(3-phenylprop-2-en-1-yl) piperazine with molecular formula $C_{26}H_{28}N_2$.its molecular weight is 368.5139.Cinnarizine inhibits contractions of vascular smooth muscle cells by blocking L-type and T-type voltage gated calcium channels. Cinnarizine has also been implicated in binding to dopamine D_2 receptors, histamine H_1 receptors, and muscarinic acetylcholine receptors.



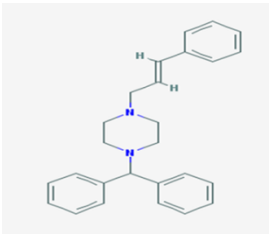


Figure 1(a): Structure of Domperidone
Figure 1(b): Structure of Cinnarizine

Aim of study

As literature survey reveals that a number of methods were reported for the estimation of these drugs in bulk and combined dosage form like Simultaneous estimation of Domperidone[5-10] and Cinnarizine[7,11-15,16] in tablet dosage form by RP-HPLC method However, these chromatographic methods lack stability indicating nature. In the present investigation, an attempt was made to develop a simple, rapid, precise and accurate stability indicating RP-HPLC assay method for simultaneous estimation of Domperidone and Cinnarizine presence of their degradation products. This proposed method can be successfully employed for quality control during manufacture and for assessment of the stability of both drugs in bulk samples and combined dosage forms.

MATERIALS AND METHODS

Drug substance

Domperidone and Cinnarizine, Orthophosporic acid (HPLC grade) and acetonitrile (70:30)(hplc grade), Waters 2695-Empower software 2.0versions.

Instrumentation

All HPLC experiments were carried out on a Waters Alliance 2695 separation module, with waters 2996 photodiode array detector in isocratic mode using Auto sampler. Data collection and processing was done using EMPOWER-PDA 2.0 software. The analytical column used for the separation was Luna C_{18} 250x4.6 mm and the other equipments used were PH meter (EUTECH),

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weighing balance (OHUS), Ultrasonicator (model UCA 701)(manufacturer Unichrome) and Pump Isocratic model.

Reagents required

Acetonitrile (HPLC grade), HPLC grade Water (MilliQ or equivalent), Ortho phosphoric acid.

Preparation of solutions

Diluent: mobile phase is used as diluent.

Preparation of ortho phosphoric acid buffer solution

Mix 1ml of ortho phosphoric acid and dissolved in 1lt HPLC grade water. Filter through 0.45µ nylon filter.

Preparation of mobile phase

Mobile phase was prepared by mixing Buffer and Acetonitrile taken in the ratio 70:30. It was filtered through 0.45µ membrane (ID 5µ particle size).

Preparation of standard stock solution

Weigh accurately about 1.85mg of Domperidone working standard and 2.46 mg of Cinnarizine working standard into a 10ml volumetric flask. Add 7 ml of diluent, sonicate to dissolve and dilute to volume with diluent. Further dilute 1 ml of above solution to 10ml with the diluent.

Chromatographic conditions

Use suitable High Performance Liquid Chromatography equipped with PDA detector.

Column : Luna C18, 250mm x 4.6mm, 5µm.

Wavelength : 226 nm

Injection Volume : 10µl

Column Temperature: Ambient

Flow rate : 1.0 ml/min

The DOMPERIDONE peak was observed at 2.525 min with peak area 1772745, tailing factor1.39. CINNARIZINE peak was observed at 5.185min, with peak area 2848084, tailing factor 1.39 and resolution 10.25. (Fig.2), (Table 2).Because of the satisfactory results, less retention time, this trial was optimized.

Retention time of Domperidone is about 2.52 min.

Retention time of Cinnarizine is about 5.18 min.

Preparation of sample solution

Weigh accurately about 23.8 mg of sample taken into a 10 ml volumetric flask. Add 7 ml of diluent, sonicate to dissolve and dilute to volume diluent. Further dilute 1 ml to 10 ml with the diluent. Filter through 0.45µ Nylon syringe filter.

Procedure

10µl of working Standard preparations were injected five times the chromatograms were recorded and peak responses were measured for Domperidone and Cinnarizine. The System suitability parameters should be meted. From the peak responses, calculated the content of Domperidone and Cinnarizine in the sample.

For Domperidone and Cinnarizine

$$\frac{AT}{AS} = \frac{\text{Std wt (mg)}}{10\text{ml}} \times \frac{1\text{ml}}{10\text{ml}} \times \frac{10\text{ml}}{\text{wt taken}} \times \frac{(P)\ \%\ \text{Potency of Std}}{1\text{ml}} \times \frac{}{100} \times 100$$

Assay (%): Assay (mg/tab) x 100 LC

Where: AT= Average area count of DOM peak in the chromatogram of sample solution.

AS= Average area count of Domperidone peak in the chromatogram of standard solution.

P=Percent potency of Domperidone working standard on as is basis.

LC= Label claim of Domperidone HCl in mg

Method Validation

The validation of HPLC method for the determination of Domperidone and Cinnarizine as per the protocol and to demonstrate that the method is appropriate for its intended use was studied for the following parameters. All the validation parameters were carried out according to ICH guidelines.

Specificity

Specificity of an analytical method is ability to measure specifically the analyte of interest without interference from blank and known impurities. For this purpose blank chromatogram, standard chromatogram and sample chromatogram were recorded. The chromatogram of blank shows no response and the results are found within the limits. The RT (min) for standard(DOM & CIN) was found to be 2.52 and 5.19.

Linearity and Range

Linear correlation was obtained between peak area v_s concentration of Domperidone and Cinnarizine were in the range of (0.37-5.55µg/ml), (2.46-36.90 µg/ml).The linearity of the calibration curve was validated by the high value of correlation co-efficient of regression equation and the results are shown in (Table- 4).

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Acceptance criteria

Correlation coefficient should be not less than 0.999.

System suitability parameters

For assessing system suitability, six replicates of working standards samples of Domperidone and Cinnarizine were injected and studied the parameters like plate number(N), tailing factor(K),resolution, relative retention time and peak asymmetry of samples. The results were show in (table-1).

Acceptance Criteria

The no. of Theoretical plates should not be less than 2000. The Tailing factor, asymmetry should not be more than 2.0 and resolution should not less than 2.

Table 1: System suitability parameters

S.No.	Name	Retention time(min)	Peak area	Tailing factor	Resolution	Plate count
1	DOM	2.52	1772745	1.37	10.25	3841
2	CIN	5.18	2840153	1.37	---	5829

Accuracy

The accuracy experiments were carried out by the standard addition method at 50%,100% and 150% levels of linearity and the recoveries obtained for Domperidone is 100.4% and for Cinnarizine is 100.5% and the results are tabulated in(Table 4).

Acceptance Criteria

The mean %recovery at each level should not be less than 98%-102%.

Precision

Precision is the degree of repeatability of an analytical method under normal operation conditions. Precision is of 3 types **(**System precision, Method precision, Intermediate precision (a. Intraday precision, b. Inter day precision).System precision is checked by using standard chemical substance. In this peak area and % of drug of six determinations is measured and % RSD should be calculated (Table 9).In method precision, a homogenous sample of single batch should be analyzed 6 times.In this analyze the sample six times and calculate the % RSD (Table 4). The precision of the instruments was checked by repeatedly injecting (n=6) solutions of 18.5µg/mL of Domperidone, 24.6µg/mL of Cinnarizine in combination).

Acceptance Criteria

The % RSD for the absorbance of six replicate injections results should not be more than 2%.

Robustness and Ruggedness

Robustness of the method was determined by carrying out the analysis at two different organic phase in mobile phase (i.e. 10±5) and three different flow rates (i.e. 1±0.2 mL/min).The high % RSD values of robustness and for Domperidone and Cinnarizine with change in flow rate. The low % RSD values of robustness and for Domperidone and Cinnarizine with change in organic phase (Table 5).Ruggedness of the method was determined by carrying out the analysis by two different time intervals and day to day and the respective peak areas were noted. The result was indicated by % RSD.

Limit of detection (LOD) and limit of quantification (LOQ)

The limit of detection (LOD) limit of quantification (LOQ) of the drug carry was calculated using the following equation as per international conference harmonization (ICH) guidelines. (LOD = 3.3 X σ /S and LOQ = 10 X σ /S).LOD for Domperidone was found to be 0.4625µg/mL and LOQ for Domperidone was found to be 0.925µg/ml, LOD for Cinnarizine was found to be 0.615 µg/ml and LOQ for Cinnarizine was found to be 1.23 µg/ml (Table 4).

Stability study

18.5µg/l of Domperidone, 24.6 µg/ml of Cinnarizine was prepared and stability study was carried out at different time intervals and the results were recorded (Table 6) and shown in fig3 (a-e).

Forced Degradation Study

Preparation of Sample Stock Solution

Weigh accurately about 23.8 mg of sample taken into a 10 ml volumetric flask. Add 7 ml of diluent, sonicate to dissolve and dilute to volume diluent. Further dilute 1 mL to 10 ml with the diluent. Filter through 0.45µ Nylon syringe filter.

Acid hydrolysis (5N HCl)

From the sample stock solution 1ml was taken into 10ml volumetric flask, add 0.1ml of 5N HCl and wait for 5mins then 0.1ml of 5N NaOH was added to neutralize the solution and diluted to volume with diluent and mixed.

Base Hydrolysis (5N NaOH)

From the sample stock solution 1ml was taken into 10ml volumetric flask, add 0.1ml of 5N NaOH and wait for 5mins then add 0.1ml of 5N HCl was added to neutralize the solution and diluted to volume with diluent and mixed.

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Oxidative Degradation (30% H2O2)

From the sample stock solution 1ml was taken in 10ml volumetric flask, adds 0.1ml of 30% H2O2 and diluted to volume with diluent and mixed.

Reduction Degradation

From the sample stock solution 1ml was taken into 10ml volumetric flask, 0.1ml of 10% sodium bi sulphate was added and then diluted to volume with diluent and mixed.

Hydrolysis Degradation

From the sample stock solution 1ml was taken in 10ml volumetric flask add 5ml of water and sonicated to disperse, dissolve and diluted to volume with diluent and mixed.

Thermal Degradation (105°C / 72 hrs)

From the sample stock solution 1ml was taken in 10ml volumetric flask, add 5ml of diluent and heated at 60°C for1 hour on a water bath. The flask was removed from the water bath and allowed to cool at room temperature and diluted to volume with diluent and mixed.

Photolytic Degradation (1.2 Million lux hours)

For the Photolytic Degradation drug sample were weighed accurately 7.5mg and transfer to petri dish. The sample was exposed to UV light in a photolytic chamber at 1.2 Million lux hours for 24 hrs. After 24hrs the sample was transferred into a 10ml volumetric flask dissolve and dilute to volume with diluent. Filter the solution using 0.45µ Nylon filter. Transfer 1ml of above stock solution into 10ml volumetric flask and make up the volume with diluent and mixed.

All the results were recorded and reported (Table 3).

RESULTS AND DISCUSSION

Optimized chromatographic conditions

Use suitable High Performance Liquid Chromatography equipped with PDA detector. Most of all reported HPLC methods till date use C_{18} column. Most of these use Complex mobile phase compositions (ortho phosphoric acid buffer and acetonitrile 70:30). Hence, attempts were directed towards development of a Simple and better method on commonly used Luna C18 column with good resolution. Different logical modifications were tried to gets good separation among the drugs and the degraded products. These changes included change in mobile phase composition in isocratic elution as well as gradient modes on different Luna C_{18} columns. The optimized chromatographic conditions (fig.2).The best peak shape and maximum separation was achieved with mobile phase consist of (OPA and acetonitrile 70:30). Peak symmetry and reproducibility were obtained on Luna C18, 250mm x 4.6mm, 5µm. The detection wavelength at 226nm, a flow rate of 1.0ml/min yielded optimum separation and peak symmetry as shown (table 2).

Chromatographic condition

Use suitable High Performance Liquid Chromatography equipped with PDA detector.

Column : Luna C18, 250mm x 4.6mm, 5µm.

Wavelength : 226 nm

Injection Volume : 10µl

Column Temperature : Ambient

Flow rate : 1.0 mL/min

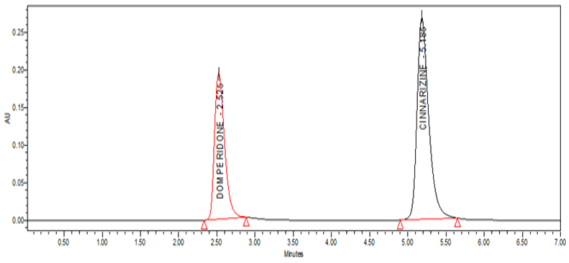

Figure 2: Optimized trial chromatogram for Domperidone and Cinnarizine

Table 2: Optimized trial results for DOMPERIDONE and CINNARIZINE

S.no	Name	Retention Time	Area	% Area	USP Plate count	USP Tailing	USP Resolution
1	DOMPERIDONE	2.525	1772745	38.36	1795	1.39	
2	CINNARIZINE	5.185	2848084	61.64	5908	1.39	10.25

Degradation studies: Results are tabulated in table no.3

Acid hydrolysis: Upon performance of acid degradation studies 28.3%of Domperidone and 25.8%of Cinnarizine was degraded.

Alkali hydrolysis: Upon performance of alkali degradation studies21 % of Domperidone and 20.4%of Cinnarizine was degraded.

Peroxide hydrolysis: Upon performance of peroxide degradation studies 21.7% of Domperidone and 24% of Cinnarizine was degraded.

Thermal degradation: Upon performance of Thermal degradation studies 22% of Domperidone and 20.6%of Cinnarizine was degraded

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Photolytic degradation: Upon performance of Photolytic degradation studies 26.5% of Domperidone and 20.2% of Cinnarizine was degraded.

Table 3: Degradation study Results of Domperidone and cinnarizine

Degradation	Sample	For CINNARIZINE		
		Mean area(n=6)	% label claim	% degradation
ACID	8.25	1139193	75	25.8
ALKALI	8.39	1248405	80.4	20.4
PEROXIDE	8.58	1252800	80	21.7
REDUCTION	8.63	1250198	79.4	21.4
HYDROLYSIS	8.41	1252800	80	20.8
THERMAL	8.55	1266727	80.2	20.6
PHOTO	8.97	1256655	80.6	20.2
Degradation	**Sample**	**For DOMPERIDONE**		
		Mean area(n=6)	**% label claim**	**% degradation**
ACID	21.6	1285513	72.2	28.3
ALKALI	26.3	1448589	79.5	21
PEROXIDE	26.39	1456880	76.5	24
REDUCTION	26.32	1451891	76.7	23.8
HYDROLYSIS	25.28	1415419	79.2	21.3
THERMAL	27.62	1466192	78.5	22
PHOTO	24.68	1464130	74	26.5

Linearity, LOD and LOQ: The calibration plot was linear over the concentration range investigated (0-5.5µg/ml; n = 3) and0-36.90µg/ml n=3) for DOM and CIN respectively (figure 4). Average correlation co-efficient r=0.9994 for DOM and 0.9992 for CIN. The LOD for DOM and CIN were found to be 0.4625µg/ml and 0.615µg/ml respectively. The LOQ that produced the requisite precision and accuracy was found to be 0.925µg/ml for DOM and 1.23µg/ml for CIN(table-4) . The regression results indicate that method was linear in the concentration range studied (table-4) and can be used for detection and quantification of DOM and CIN in a very wide concentration range.

Accuracy and Precision: Accuracy as recovery was evaluated by spiking previously analyzed test solution with additional Standard drug at three different concentration levels (table-4). Recovery of standard drugs added was found to be 100.4% for DOM and 100.5% for CIN with the value of RSD less than 1% indicating that the proposed method is accurate for the simultaneous estimation of both drugs from their combination drug products in presence of their degradation products. The low RSD values indicate the repeatability and reproducibility of the Method (table-4).

Table 4: Results of linearity for DOM and CIN

PARAMETERS	DOMPERIDONE	CINNARIZINE
Linearity range(µg/ml)	0-5.5	0-36.90
Regression equation	y=441794x+15629	y=108693x+23225
slope	441793.83	108692.62
intercept	15628.88	23225.43
Correlation coefficient (r^2)	0.9994	0.9992
Accuracy (%Recovery)	100.4	100.5
System Precision (RSD)	0.611	0.173
Method precision(RSD)	0.33	0.34
LOD (µg/ml)	0.4625	0.615
LOQ (µg/ml)	0.925	1.23

Robustness: Results of the robustness study are depicted in Table no.5. The elution order and resolution for both components were not significantly affected. RSD of peak areas were found to be well within the limit of 2.0%.

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Table 5: a. Robustness results of Domperidone by RP-HPLC:

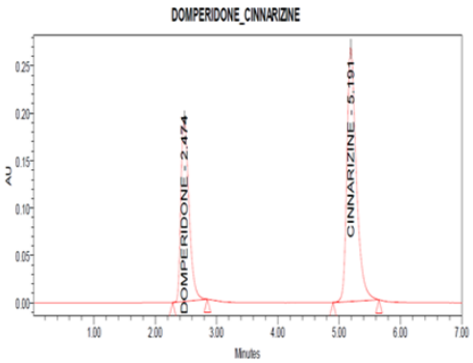
Parameter	DOMPERIDONE					
	Retention time(min)	Peak area	Resolution	Tailing	Plate count	% RSD
Organic Plus	2.430	2002108	--	1.39	3569	0.41
Organic Minus	2.500	1740390	--	1.43	3919	0.47
Flow Plus	2.032	1525220	--	1.40	3766	0.2
Flow Minus	3.127	1904992	--	1.41	2849	0.45
Parameter	**CINNARIZINE**					
	Retention time(min)	**Peak area**	**Resolution**	**Tailing**	**Plate count**	**% RSD**
Organic Plus	4.668	3013545	9.29	1.57	7149	0.47
Organic Minus	6.095	3139136	13.06	1.39	6691	0.12
Flow Plus	4.417	2549813	11.59	1.48	7325	0.38
Flow Minus	6.412	4179772	11.10	1.51	5798	0.25

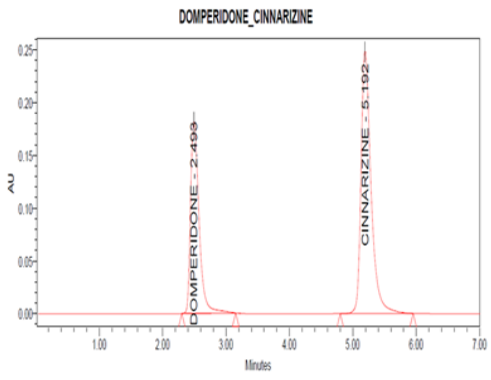
Ruggudness: The mean of Domperidone and Cinnarizine is 1760858 and 2845499 and the percentage RSD was found to be 0.32 and 0.25%.

Table 6: Results of stability study

Stability study results of DOM & CIN

Time period (hours)	For Domperidone				
	Retention Time(min)	Peak Area	Tailing Factor	Plate Count	
0	2.474	1765360	1.43	1689	
6	2.477	1866612	1.33	3886	
12	2.466	1850654	1.41	3835	
18	2.463	1828447	1.42	3874	
24	2.493	1700383	1.49	3814	
Time period (hours)	**For Cinnarizine**				
	Retention Time(min)	**Peak Area**	**Tailing Factor**	**Plate Count**	**Resolution**
0	5.191	2843148	1.41	5840	10.43
6	5.188	2993581	1.40	5902	10.51
12	5.182	2973773	1.42	5923	10.58
18	5.182	2952000	1.41	5903	10.48
24	5.192	2709577	1.46	5745	10.37





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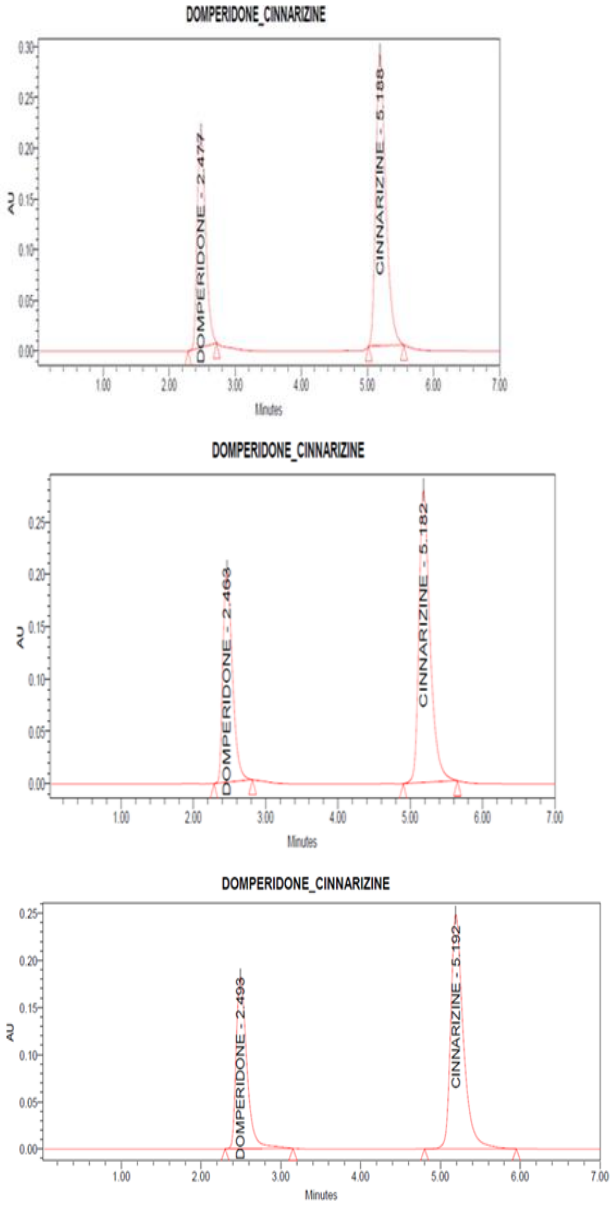

Figure 3: (a) chromatogram at 0 hrs (DOM & CIN) (b) chroatogram at 6hrs (DOM & CIN) (c) chromatogram at 12hrs (DOM & CIN) (d) chromatogram at 18hrs (DOM & CIN) (e) chromatogram at 24hrs (DOM & CIN)

SUMMARY

An attempt has been made to develop a new stability indicating validated RP-HPLC method for the simultaneous estimation of DOM and CIN in bulk and in dosage form. As the literature survey revealed that only two methods are available for estimation of DOM and CIN in bulk and in dosage forms so there is a need for a simple, economical and proper method of estimation of DOM and CIN bulk and in dosage form.

The estimation of DOM and CIN was carried out by using Luna C18 250x4.6 mm,5µmcolumn combined with PDA detector with a flow rate of 1ml/min and an injection volume of 10µlwas injected and eluted with the mobile phase containing Buffer and Acetonitrile (70:30v/v) as mobile phase. The peaks of DOM and CIN were eluted at retention times of 2.525 and 5.185 min respectively.

After optimizing the method, it was validated for system suitability, specificity and linearity, sensitivity parameters, precision, accuracy and robustness studies as per ICH guidelines. The results for validation parameters were within the limits. For assay RSD values were <2. Recoveries were in the range of 98%-102%.

CONCLUSION

The proposed RP-HPLC method was simple, rapid, accurate, precise, specific, robust and economical and less time consuming. so it is considered as a method of choice for the determination of Domperidone and Cinnarizine combination dosage forms. All the parameters of developed method met the criteria of ICH guidelines for method validation.

The developed HPLC method has the following advantages:

1. No tedious extraction procedures were involved.
2. These methods are also having an advantage than reported method of good resolution and with retention time.
3. The developed method has good recovery and sensitivity.
4. The run time required for recording chromatogram was below 8.0 mins.
5. Suitable for the analysis of bulk drug and formulations.

REFERENCES

1. Available from: http://www.drugbank Domperidone.
2. Available from: http://www.drugbank Cinnarizine.
3. Available from: http://en. wikipedia.org/wiki/Domperidone.
4. Available from: http://en.wikipedia.org/wiki/Cinnarizine.
5. Sharma Suparna, Sharma Anuj Kumar, Singh Ompal, Chaturvedi Ashwani Kumar, Verma Vikrant, Arya Rajat Kumar, Singh Umesh Kumar, RP-HPLC method development and validation of Domperidone in solid dosage form, The pharma innovation, 1, 2012, 16-20.
6. Sohan S. Chitlange, Amir I. Mulla, Ganesh R. Pawbake and Sagar B. Wankhed, A validated RP-HPLC method for simultaneous estimation of Dexrabeprazole and Domperidone in pharmaceutical dosage form, Der Pharmacia Sinica, 1, 2010, 42-47
7. Kalyankar T. M, Kulkarni P D, Panchakshari P. P, Narute A. S,Simultaneous RP-HPLC estimation of Cinnarizine and Domperidone in tablet,Research journal of pharmacy and technology, 7, 2014, 650-654.
8. Sivakumar Thanikachalam, Manavalan Rajappan Valliappan, Kannappan, Stability indicating HPLC method for simultaneous determination of Pantaprazole and

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Domperidone from their combination drug product,Infona portal, 67, 2008, 41–47.

9. Ram S. Sakhare, Sanjay S. Pekamwar, Sujata Dhamne, Development and validation of stability indicating HPLC methods for simultaneous estimation of Ilaprazole and Domperidone in bulk and solid dosage form, International research journal of pharmacy, 41, 2016, 116-120.
10. Bhavesh Patel, Madhabhai Patel, Jignesh Patel & Bhanubhai Suhagia, Simultaneous Determination of Omeprazole and Domperidone in Capsules by RP-HPLC and Densitometric HPTLC, Journal of Liquid Chromatography & Related Technologies, 30, 2007, 1749-1762.
11. S. Khushbu and P. Pinkal, Development and validation of analytical method for simultaneous estimation of Cinnarizine and dimenhydrinate in tablet dosage form, International journal of pharmaceutical sciences and research, 5, 2015, 4815-4819.
12. Naga sirisham. M, shantha kumara A,validated RP-HPLC method for simultaneous estimation of Cinnarizine and Domperidone in bulk and pharmaceutical dosage form, journal of pharmaceutical and scientific innovation, 2, 2013, 46-50.
13. A.A. heda, A. R. sonaware, G.H. naranje,P. K. puranika A, Rapid Determination of Cinnarizine in Bulk and Pharmaceutical Dosage Form by LC,E-journal of chemistry, 7, 2010, 1080-1084.
14. Ruchitha J. CHAUHAN, T.Y. Pasha, Stavan M, Khushbu A. Thakor, Parth. U Patel, Development and validation of RP-HPLC method for Development and Validation of Stability Indicating Analytical Method for Cinnarizine and paracetamol in their pharmaceutical dosage form, International bulletin of drug research,4,)2014,41-52.
15. A. Prameela Rani, K.E. Pravallika, P. Ravi, O. Sasivardhan, Development and Validation of Stability Indicating RP-UPLC Method for the Simultaneous estimation of Chlordizepoxide and Amitriptyline Hydrochloride in Bulk and Tablet Dosage Forms, international journal of chemtech research, 10, 2017, 467-476.
16. Amal B ahmed, nada s abdelwahabad, maha M abdelrehman, fathy M salma, Simultaneous determination of Dimenhydrinate, Cinnarizine and Cinnarizine impurity by TLC and HPLC chromatographic methods, bulletin of faculty of pharmacy, 55, 2017, 163-169.

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