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Research Article

STUDY OF DRUG-DRUG INTERACTION AND SIMULTANEOUS ESTIMATION OF A NEW COMBINATIONAL DRUG BY DSC AND HPLC

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ABSTRACT

It is a common practice in medical science to prescribe more than one drug. One drug may interact with another drug or foods which causes serious side effects in human health. In lieu of administrating individual drug it's better to take developed combinational drug. This study observed the interaction of individual drugs in two homogeneous multi mixture A and B by DSC and HPLC at 1:1 molar ratio. A new RP-HPLC methodalso developed and validated for a combinational drug of valsartan and ciprofloxacin HCl. The DSC thermo gram of mixture-A (valsartan, naproxen, lercanidipine, cefepime and metformin HCl) and mixture-B (ramipril, naproxen, lercanidipine, ciprofloxacin HCl and gliclazide BP) shown sharp melting endotherm at 62.90°C, 104.05°C & 327.86°C and at 59.77°C & 105.51°C respectively. In HPLC, only one retention time found at 6.431 ± 0.1 for mixture-A and two retention time at 6.373 ± 0.1 and 7.196 ± 0.1 for mixture-B, under the condition of 2% acetic acid (PH 2.70) and acetonitrile (30:70, v/v) at 215nm and 254nm. But at same condition when the 5% acetic acid (PH 3.45) used, no sharp peaks observed for both mixtures. That indicates strong interactions due to bond breaking and forming among the drugs. Second,for simultaneous estimationof a combinational drug of ciprofloxacin HCl and valsartan, the retention times found at 2.770 ± 0.1 min and 8.647 ± 0.1 min, the correlation coefficient found at 0.9991 and 0.9993 and the percentage recovery found 98.48% and 101.70%, respectively, under the condition of 2% acetic acid (PH 2.70) and acetonitrile (40:60, v/v) at 240nm. The % RSD values found for ciprofloxacin HCl as 0.80-1.83 and valsartan as 0.41-1.33 by observing both intra and inter day.

Keywords: *In vitro*, Drug-Drug Interaction, Valsartan, Ciprofloxacin HCl, DSC, HPLC.

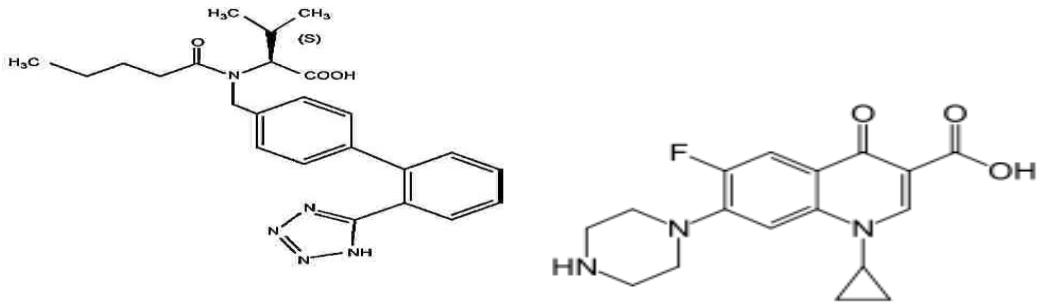
INTRODUCTION

Now-a-days, patients are attacked in inflammation, diabetic, hypertension, kidney or heart failure at a time and as a rescue medical science prescribed more than one drug at a time. Moreover, mineral supplements along with drug therapy are also a common and useful practice (Saha *et al.,* 2012). The drugs administrating at a time may exhibit impacts independently or interact with each other. The interaction may be agonist or antagonist of one drug by another (Saha *et al.,* 2013). The combination therapies are beneficial to the patients but sometimes it also causes serious negative effects in human body (Ahsan *et al.,* 2011; Brunton *et al.,* 2005 and R. *et al.,* 2008). Therefore; drug interactions definitely alter the pharmacological effects. The interaction may declinethe patient's clinical status and possibly life-threatening or lead to permanent damage (Kundu *et al.,* 2012 and Ahsan *et al.,* 2012).

An administered druginteraction with food staffs and different components of body may form complex species whichmay possibly harmful or harmless. Confrontational drug interactions cause a loss in therapeutic activity, toxicity or unexpected increase in pharmacological activity of a drug (Kristensen *et al.,* 1976; Mohiuddin *et al.,* 2009 and Brouwers *et al.,* 1992).

Knowledge of drug interaction may allow early recognition and prevention of adverse consequences. The most comprehensive understanding of clinically significant drug interaction can be achieved by combining knowledge of the mechanism of drug interaction with recognition of the high-risk patients and the identification of drug with a narrow therapeutic index (Hansten *et al.,* 1989).

The target of this research work is to find out the drug-drug interaction among anti-hypertensive, anti-diabetic and anti-bacterial drugs and concurrent estimation of a combinational drug of valsartan (Criscione *et al.,* 1995; Psaty *et al.,* 1997 and Cohn *et al.,* 2001) and ciprofloxacin HCl (Ciprofloxacin-Hydrochloride, 2011; Cooper *et al.,* 2005 and Zehnder *et al.,* 1995) by development and validation of a new RP-HPLC technique.



(A) (B)

Figure 1: Structure of Valsartan (A) and Ciprofloxacin HCl (B).

METHODS AND MATERIALS

Drugs and reagents used

The used drugs naproxen (Potency: 99.90%), Lercanidipine (Potency: 99.05%), Cefepime (Potency: 97.86%), Metformin HCl (Potency: 99.49%), Ramipril (Potency: 99.70%), Gliclazide BP (Potency: 99.29%), Glimepiride (Potency: 95.41%), Ciprofloxacin HCl(Potency: 84.23%) and valsartan (99.9%) werecollectedfor this study from Drug International Ltd., Dhaka, Bangladesh and reagents of HPLC grade acetonitrile, methanol, ethanol and acetic acid glacial were purchased from Active Fine Chemicals Ltd., Dhaka, Bangladesh.

Instrument used

Drug-drug interaction and simultaneous estimation of combinational drug was analyzed with Differential Scanning Calorimeter (DSC) (Model: DSC-60 WS, Shimadzu Corporation, Japan) and High Performance Liquid Chromatography (HPLC) (UFLC Prominence, Shimadzu Corporation, Japan) which equipped with an auto sampler (Model-SIL 20AC HT) & UV-Visible detector (Model-SPD 20A).DSC was used for recording thermo grams and in case of HPLCchromatogram was recorded using LC-solutions software. A phenomenexcolumn Carbon-18 (4.60 × 250mm, 5µm) was used during HPLC analyses.

EXPERIMENTATIONS

DSC Method

5 mg from each drug of mixture A (Valsartan, Naproxen, Lercanidipine, Cefepime and Metformin HCl) and mixture B (Ramipril, Naproxen, Lercanidipine,Gliclazide BP and Ciprofloxacin HCl) was weighted by using weight balance and mixed properly to make a solid homogeneous mixture in a watch glass.

2.40 mg and 2.10 mg of mixture-A and mixture-B were weighted from solid homogeneous mixture respectively and sealed into aluminum pans. In similar way standard sample pans also prepared. Analysis of mixture-A, mixture-B and standards were performed at a flow rate of 20mL/min under nitrogen gas at temperature range30°C to 350°Cand increase in heat by 10°C/ min.

HPLC Method

5 mg from solid homogeneous mixture of mixture-A was weighted and taken into a test tube and dissolved in methanol. Similarly, mixture-B was dissolved in ethanol after

weighted 5 mg from solid homogeneous mixture of mixture-B.The sample mixtures were filtered using 0.45 µmsyringe filter and filled the vials. In similar way standard sample vials also prepared. The injection volume during all analysis was kept at 20 µL.

20 mL of acetic acid glacial was taken and added distilled water up to 1000 mL to prepare solution of 2% acetic acid and maintained the pH to 2.70 by using pHmeter. 5% acetic acid glacial (pH3.45) was prepared in same way.

A mobile phase comprising of 2% acetic acid (PH 2.70) & acetonitrile (30:70, v/v) and 5% acetic acid (P^H 3.45) and acetonitrile (30:70 v/v) with flow rate 0.70 mL/min at wavelength 215 nm and 254 nmwas maintained for drug-drug interaction. For simultaneous determination of combinational drug the mobile phase of 2% aqueous solution of acetic acid and acetonitrile in the ratio of 40: 60 (v/v) with a flow rate of 0.70 mL/min and wavelength 240 nm at ambient temperature under isocratic condition was maintained.

In case of simultaneous estimation of combinational drug specificity, linearity, accuracy/ percentage (%) recovery and precision/reproducibility or percentage (%) RSD was studied. For linearity, five different concentrations 40, 45, 50, 55 and 60 µg/mL was analyzed. For study of accuracy/ percentage (%) recovery 34, 36 and 38µg/mL and reproducibility/ percentage (%) RSD 42, 44 and 46µg/mL concentrations were analyzed.

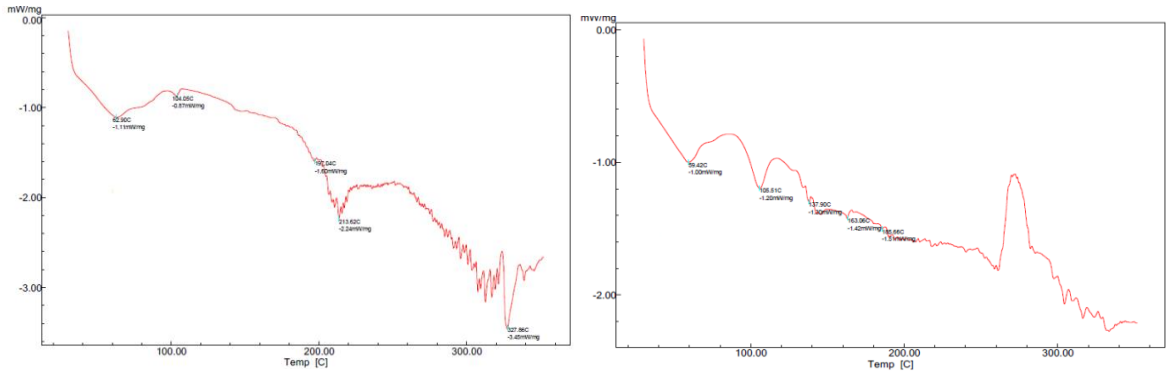
100µg/mL standard solution for valsartan and ciprofloxacin was prepared by taking equivalent amount of 30mg drug into a 100 mL volumetric flask separately and dissolved withacetonitrile and distilled water (50:50). To prepare a 100µg/mLmixed solution of valsartan and ciprofloxacin HCl, 50 mL from each solution was taken into a volumetric flask and mixed properly.Then 34, 36, 38, 40, 42, 44, 45, 46, 50, 55, 60µg/mL solution were prepared from this mixed solution by taking 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.5, 4.6, 5.0, 5.5, 6.0 mL into 100 mL volumetric flask and up to the marked with acetonitrile and distilled water (50:50).

RESULT AND DISCUSSION

DSC Method

A clear indication of interaction was studied for mixture-A (valsartan, naproxen, lercanidipine, cefepime and metformin HCl) and mixture-B (ramipril, naproxen, lercanidipine,gliclazide BP and ciprofloxacinHCl) by differential scanning calorimeter (DSC) at the temperature range of 30°C to 350°C with molar ratio 1:1. The DSC thermo gram was also taken for individual drug. The DSC thermo gram of mixture-A shown sharp melting endotherm at 62.90°C, 104.05°C and 327.86°C corresponded to its melting normalized energy of -1.11mW/mg, -0.87mW/mg and -3.45mW/mg, respectively. The melting endotherm for valsartan at 117°C, lercanidipine at 121°C, naproxen at 156.61 °C, metformin

HCl at 233.03°C and cefepime at 150°C. The melting endotherm of mixture-A and standard were not identical.This might be due to the bond forming of new productsbythe interactions among drugs. DSC thermo gram of mixture-B shown sharp melting endotherm at 59.77°C and 105.51°C corresponded to its melting normalized energy of -1.00mW/mg and -1.20mW/mg, respectively. The melting endotherm for ramipril at 109°C, lercanidipine at 121°C, naproxen at 156.61°C, ciprofloxacin HCl at 152.65°C and gliclazide BP at 169.38°C. The melting endotherm of mixture-B and standard drugs also showed different. Different melting endotherm represented the identity of new products and it might be due to the interactions among the drugs.



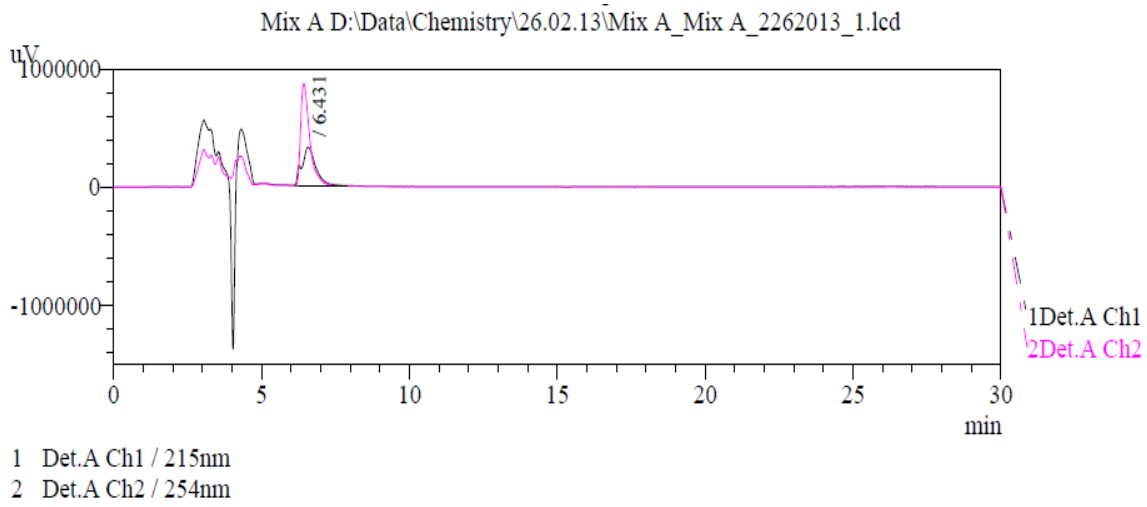
(A) **(B)**

Figure 2: The DSC thermogramof mixture-A (A) andmixture-B (B) at 1:1 ratio.

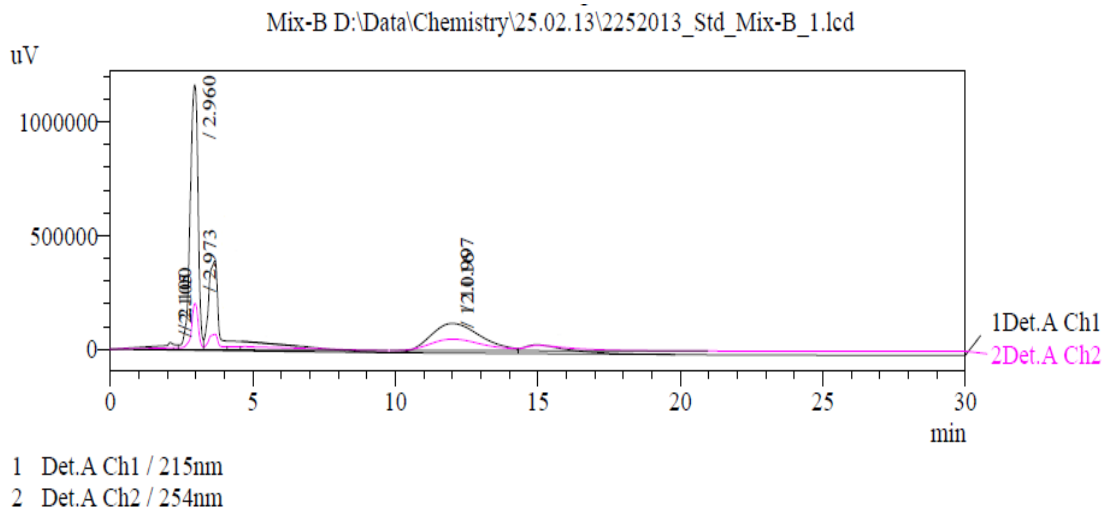
HPLC Method

For the study of drug interaction chromatogram was taken for mixture-A (valsartan, naproxen, lercanidipine, cefepime and metformin HCl) and mixture-B (ramipril, naproxen, lercanidipine,gliclazide BP and ciprofloxacinHCl) in HPLC. Analysis were ran under the conditions: 2% acetic acid (P^H 2.70) and acetonitrile (30:70, v/v) and 5% acetic acid (P^H 3.45) and acetonitrile (30:70, v/v), UV was 215 nm and 254 nm, total flow rate was 0.70 mL/min, pressure 116 kgf. For mixture-A, the retention time was observed at 6.431 ± 0.1(Figure 3) and for mixture-B, at 6.373 ± 0.1 and 7.196 ± 0.1(Figure 3), under the condition of 2% acetic acid (P^H 2.70) and acetonitrile (30:70, v/v). When the mobile phase was 5% acetic acid (P^H 3.45) and acetonitrile (30:70, v/v) at same other conditions, there was no sharp peaks observed (Figure 4). The chromatogram was also taken for the standard drugs valsartan, naproxen, lercanidipine, cefepime, metformin HCl, gliclazide, ciprofloxacin HCl and glimepiride andretention times observed at 6.449 ± 0.1 min, 6.343 ± 0.1, 3.081 ± 0.1, 4.455 ± 0.1, 2.808 ± 0.1, 7.167 ± 0.1, 2.859 ± 0.1, 13.715 ± 0.1 min, respectively. Mixture-A and mixture-B both were combined of five drugs each. But there was only one peak for mixture-A and two for mixture-B (Figure 3).That might be due to bond breaking and forming among

the drugs. So it might be concluded that, there were strong interactions among the drugs in both mixtures.

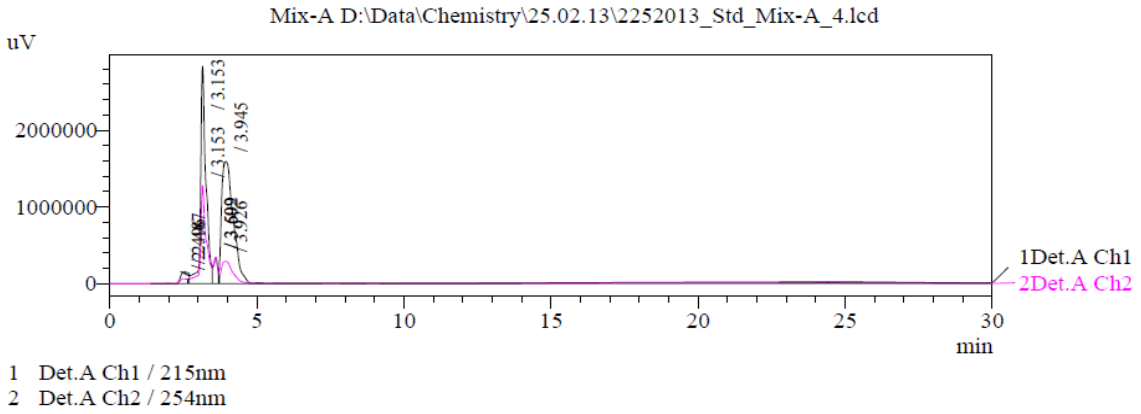


(A)

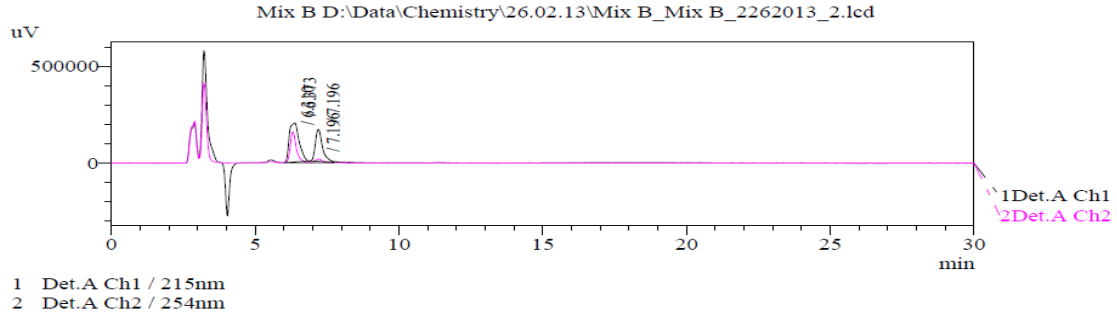


(B)

Figure 3: The HPLC chromatogram of mixture-A (A)and mixture-B in 2% acetic acid and acetonitrile (30:70, v/v) (B).



(A)



(B)

Figure 4: The HPLC chromatogram of mixture-A (A) and mixture-B (B) in 5% acetic acid and acetonitrile (30:70, v/v).

Ananti-hypertensive drug valsartan and anti-inflammatory drug ciprofloxacin HCl was combined at different chromatographic conditions [like changing mobile phase, UV wavelength and flow rate] for simultaneous estimation of a combinational drug. The peak areas were found sharp and resolution was also good (Figure 5) using the mobile phase of 2% aqueous solution of acetic acid and acetonitrile in the ratio of 40: 60 (v/v) with a flow rate of 0.70 mL/min and wavelength 240 nm at ambient temperature. The retention times observed for standard ciprofloxacin HCl and valsartan at 2.770 ± 0.1 min and 8.647 ± 0.1 min, respectively and observedfor mixed ciprofloxacin HCl and valsartan at 2.769 ± 0.1 min and 8.657 ± 0.1 min, respectively (Figure 5). This almost identical result confirmed that there mightnotany drug-drug interaction. The absence of interaction was confirmed by specificity**,** linearity, accuracy/percentage recovery and reproducibility on intra & inter day.

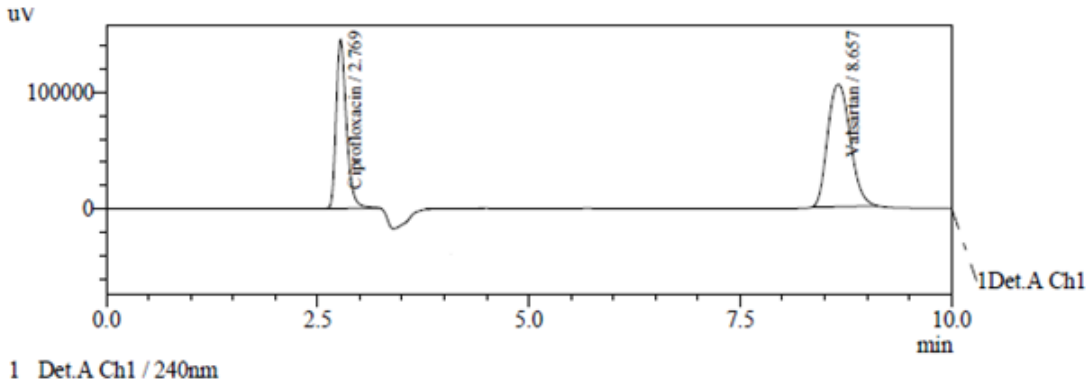


Figure 5: Chromatogram for ciprofloxacin and valsartan.

Specificity was checked by collecting anti hypertensive drug and anti inflammatory drug from market containing valsartan and ciprofloxacin HCl. Both drug was mixed and analyzed where no peak was observed except for valsartan and ciprofloxacin HCl. The high degree of specificity was proved from this observation.

The linearity was studied at five different concentrations 40µg/mL, 45µg/mL, 50µg/mL, 55µg/mL and 60µg/mL. A calibration curve was found when peak areas plotted against those concentrations. The slope (m) and intercept (c) of the calibration curve for ciprofloxacin HCl and valsartan calculated at 32198.64 & 95376.2 and 60922.96 & -264759, respectively (Table 1, Figure 6). A good correlation coefficient (r2) found at 0.9991 and 0.9993 for ciprofloxacin HCl and valsartan was within acceptable range of guidelines.

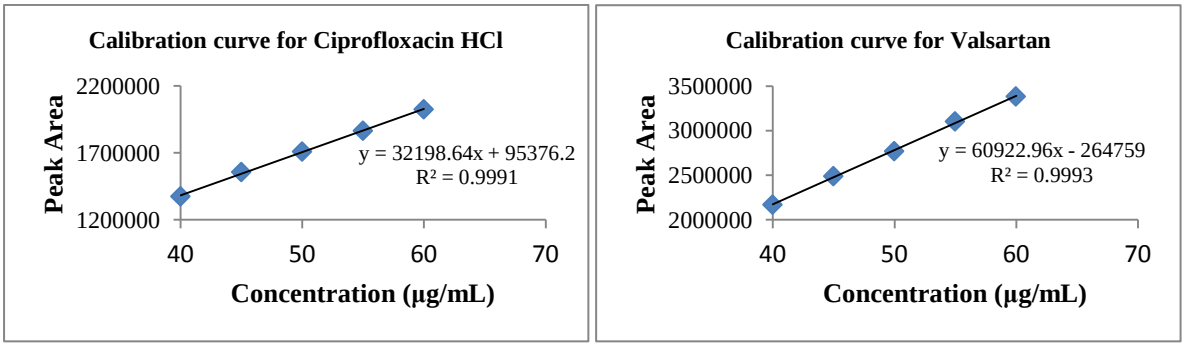


Figure 6: Calibration curve and linearity of ciprofloxacin HCl and valsartan.

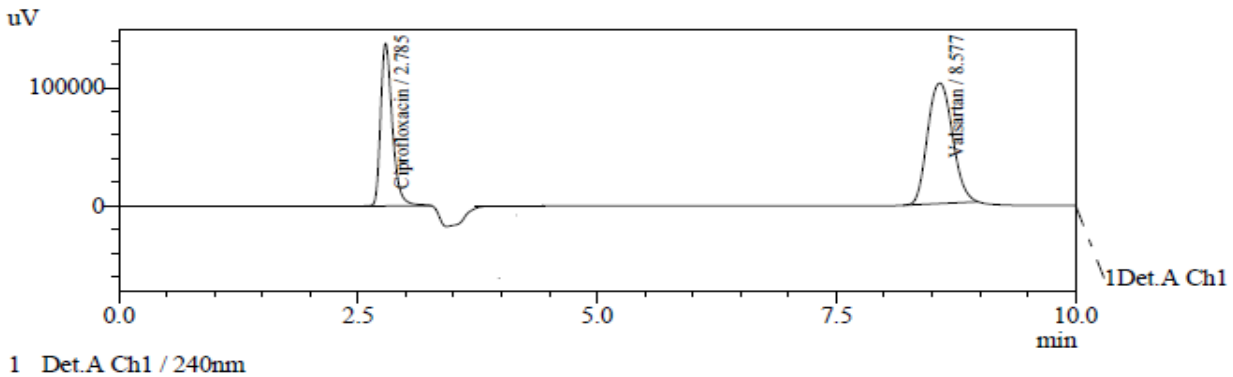
Table 1: Peak area at various Concentrations forCiprofloxacin HCl and valsartan.

		Ciprofloxacin HCl	Valsartan
Parameters	**Concentration (µg/mL)**	**Peak Area**	**Peak Area**
Linearity	40	1373846	2168012
	45	1555455	2486791
	50	1708820	2766916
	55	1863761	3101487
	60	2024659	3383738

The accuracy expressed as percentage of recovery was evaluated at three different concentrations 34µg/mL, 36µg/mL and 38µg/mL (Table 2, Figures 7)., The percentage (%) of recovery found 98.38, 98.14 and 98.92 for ciprofloxacin HCland 101.54, 101.13 and 102.43 for valsartan at 34µg/mL, 36µg/mL and 38 µg/mL, respectively (Table 2) was also in acceptable range (97-103).

Table 2: Data for accuracy/ recovery of ciprofloxacin HCl and valsartan in spikes.

		Ciprofloxacin HCl		Valsartan	
	Concentration (µg/mL)	**Peak Area**	**% Recovery**	**Peak Area**	**% Recovery**
Accuracy	34	1172451	98.38	1845821	101.54
	36	1233050	98.14	196976	101.13
	38	1305706	98.92	2125565	102.43



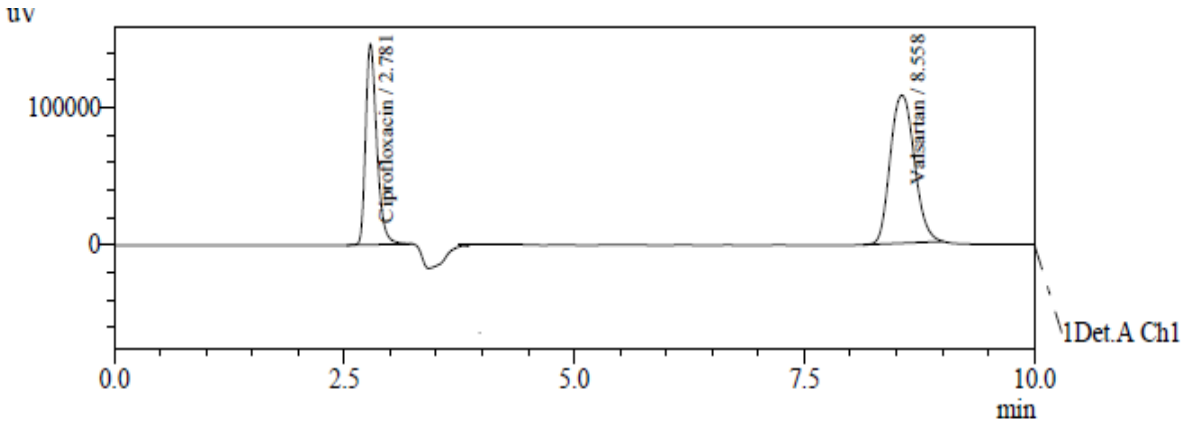
1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.785	1172451	2403.380	1.434	0.000
Valsartan	8.577	1845821	5280.126	1.137	16.565
		3018273			

(A)



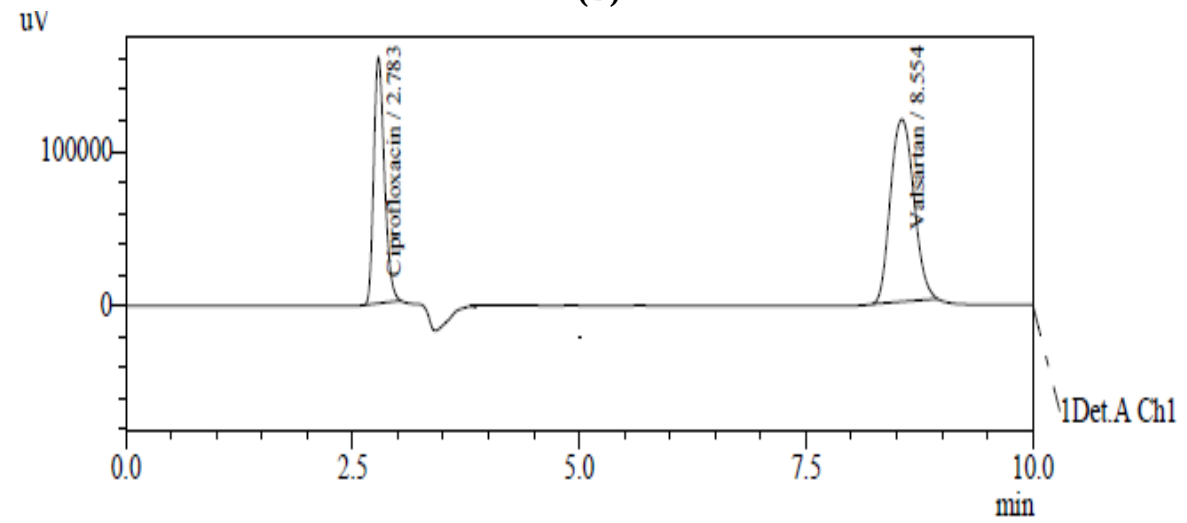
1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.781	1233050	2409.909	1.413	0.000
Valsartan	8.558	1968976	5216.703	1.160	16.492
		3202026			

(B)



1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.783	1305706	2457.504	1.343	0.000
Valsartan	8.554	2125565	5300.699	1.139	16.619
		3431272			

(C)

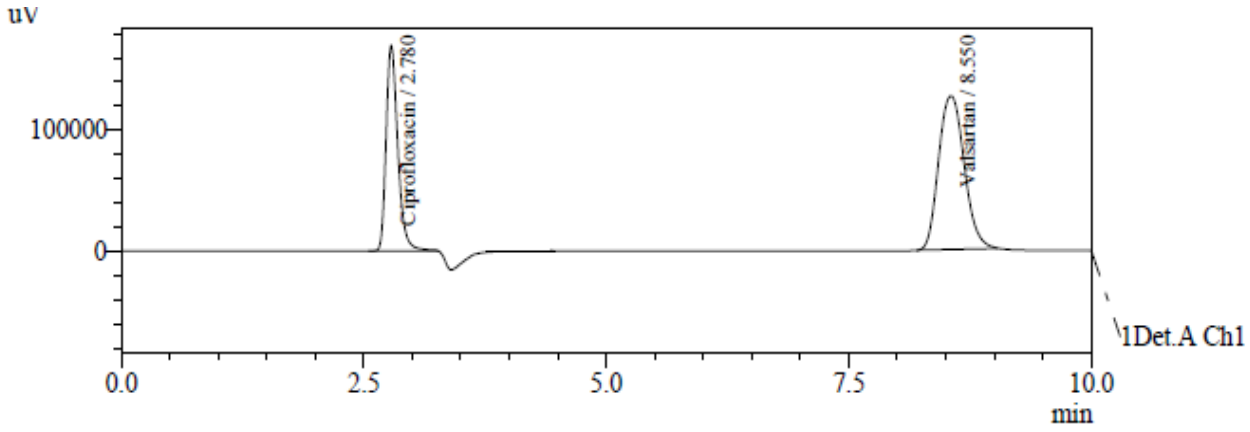
Figure 7: Chromatogram for accuracy at concentration of 34 µg/mL (A), 36 µg/mL (B) and 38µg/mL (C) for Ciprofloxacin HCL and Valsartan.

The precision/ reproducibilitywere checked by intra-day (Table 3, Figure 8) and inter-day repeatability of responses (Table 4) atthree different concentrations 42, 44 and 46µg/mL. Percentage(%) RSD value on intra-day analysis was found for ciprofloxacin HCl at 0.98, 1.83 and 0.80 and for valsartan at 0.84, 0.41 and 1.33 in concentrations 42, 44, 46µg/mL, respectively (Table 3).In both cases, % RSD values were within the limit (less than equal two).

Table 3: Intra-day precision/ reproducibility for ciprofloxacin HCl and valsartan

	Ciprofloxacin HCl			**Valsartan**		
Concentration (µg/mL)	**Peak Area**	**% RSD**	**% Recovery**	**Peak Area**	**% RSD**	**% Recovery**
42	1434440	0.98	99.02	2331769	0.84	99.16
44	1486169	1.83	98.17	2404859	0.41	99.59
46	15645944	0.80	99.20	2500253	1.33	98.67

[%RSD = (Standard deviation/mean) x 100%]



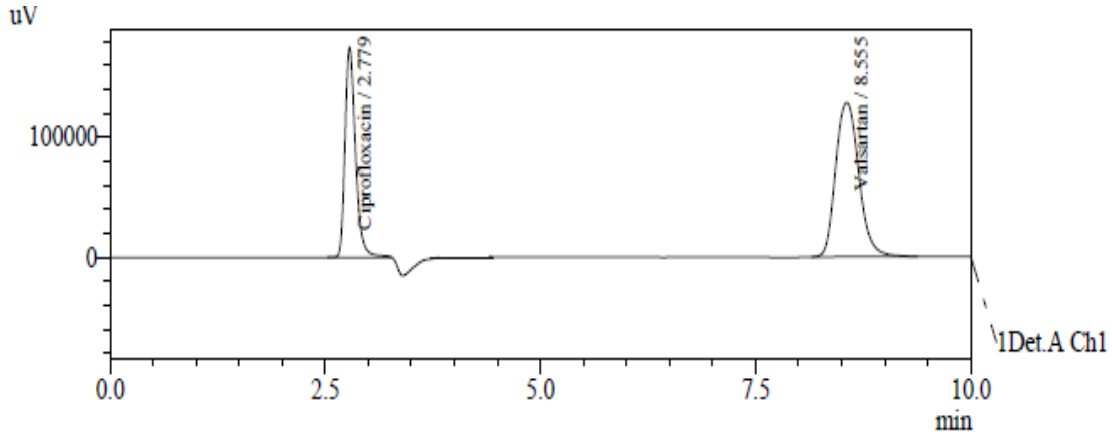
1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.780	1434440	2457.148	1.387	0.000
Valsartan	8.550	2331769	5203.233	1.176	16.524
		3766209			

(A)



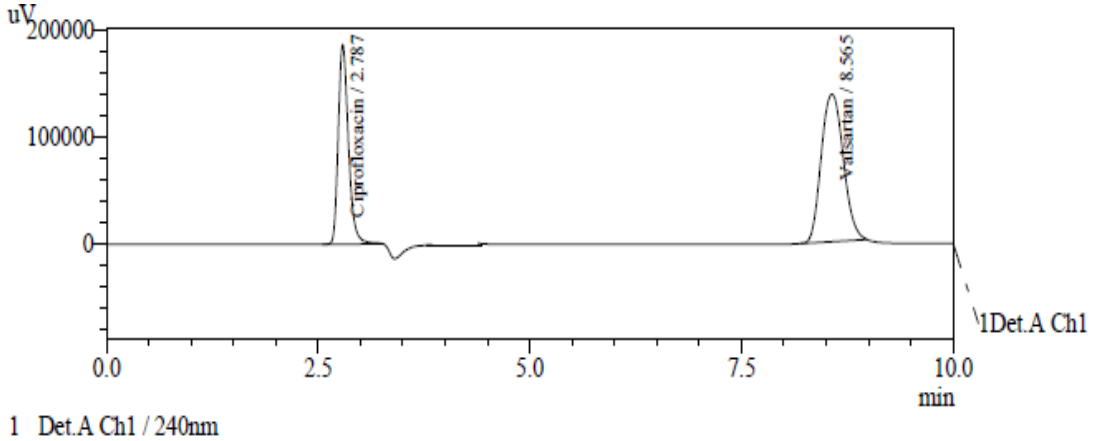
1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.779	1486169	2426.661	1.379	0.000
Valsartan	8.555	2404859	5134.265	1.207	16.426
		3891028			

(B)



1 Det.A Ch1 / 240nm

PeakTable

Detector A Ch1 240nm

Name	Ret. Time	Area	Theoretical Plate	Tailing Factor	Resolution
Ciprofloxa	2.787	1564594	2463.524	1.353	0.000
Valsartan	8.565	2500253	5247.260	1.149	16.565
		4064847			

(C)

Figure 8: Chromatogram for reproducibility at concentration of 42 µg/mL (A), 44 µg/mL (B) and 46µg/mL (C) for Ciprofloxacin HCL and Valsartan.

The average % recovery was found on inter-day analysis for ciprofloxacin HCl98.16, 99.57 and 98.64 on 1st day, 2nd day and 3rd day, respectively.For valsartan the average % recovery was found 100.78, 100.18 and 100.19 on 1st day, 2nd day and 3rd day, respectively (Table 4). In both average % recovery values were within the limit (98-103%).

Table 4: Inter-day Precision/ Reproducibility of ciprofloxacin HCl and valsartan

Drug	**Injected Concentration (µg/mL)**	**% Recovery**			**Average % Recovery**
		Day-1	**Day-2**	**Day-3**	
Ciprofloxacin HCl	42	98.14	98.21	98.14	98.16
	44	99.61	99.70	99.41	99.57
	46	98.67	98.64	98.61	98.64
Valsartan	42	100.84	101.12	100.39	100.78
	44	100.18	100.18	100.18	100.18
	46	99.45	100.73	100.11	100.19

The specificity**,** linearity, accuracy/percentage recovery and reproducibility on intra &inter day values were within limit of guidelines and no interaction present between those drugs. So a simple and accurate RP-HPLC method was developed and validated for a simultaneous estimation of a combinational drug of valsartan and ciprofloxacin HCl.

CONCLUSION

In course of research works, anti-diabetic, antibiotic and anti hypertensive drugs were analyzed to study the interaction among the drugs. For study and detection of drug- drug interaction a reliable DSC (Differential Scanning Calorimeter) method and HPLC method were used. Both enthotherm and chromatogram showed strong interaction among the drugs.This study also found no interaction between anti-hypertensive drug valsartan and anti-inflammatory drug ciprofloxacin HCl by HPLC. The specificity, linearity, accuracy, precision and percentage recovery values found within acceptable range which confirmed that there was interaction between those drugs and a new RP-HPLC method is developed and validated for simultaneous estimation of a combinational drug of valsartan and ciprofloxacin HCl.Since, the administration of developed combinational drug can reduce the side effects in human body, so it’s better to take combinational drugs instead of more than one single drug at a time.

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