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Box Behnken Design (BBD) Application for Optimization of Chromatographic Conditions in RP-UPLC Method Development for Simultaneous Determination of Paracetamol, Cetirizine and Phenylephrine in Api and Tablet Dosage Forms

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KEYWORDS
Paracetamol
Cetirizine
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RP-UPLC

ABSTRACT:

Introduction: An accurate, quick, and precise reversed phase UPLC technique has been created to determine the pure concentrations of phenylephrine(phy), cetirizine(ctz), and paracetamol(para) with a box behnken design (BBD) application. BBD was employed to optimize the chromatographic conditions for analytical methods.

Objectives: The purpose of this work is to create a stability-indicating reverse phase UPLC method and validate it according to ICH Q2(R1) guidelines. that will fill a research gap as it enhances the three parameters i.e. speed, resolution, and sensitivity.

Methods: RP-UPLC method was carried out by pumping Mobile phase at a flow rate of 0.3 ml/min i.e. methanol and buffer in a ratio of 55:45 A. This approach employed K_3PO_4 as a buffer. A constant 24°C temperature was maintained. 280 nm was the optimal wavelength for paracetamol, cetirizine, and phenylephrine.

Results: The retention durations for phenylephrine, cetirizine and paracetamol were determined to be 1.895, 1.173, and 0.710 minutes, respectively. It was identified that the % RSD of the system precision for phenylephrine, cetirizine, and paracetamol was 0.4,0.3, 0.4 and method precision was identified to be 0.2, 0.4 and 1.1 respectively. The percentage recovery for paracetamol, cetirizine, and phenylephrine was found to be 100.40%, 99.73% and 100.12%, respectively. The regression equations for paracetamol, cetirizine, and phenylephrine yielded LOD and LOQ values of 1.26 µg/ml, 0.07 µg/ml, 0.02 µg/ml, 3.83 µg/ml, and 0.21 µg/ml, 0.05 µg/ml, respectively. The regression equations for cetirizine (y = 19458x + 602.07), phenylephrine (y = 19316x + 797.53), and paracetamol (y = 18109x + 8212.5) were found.

Conclusions: A simple, Accurate, precise method was developed for the simultaneous estimation of the paracetamol, cetirizine and phenylephrine in solid dosage form. The %RSD of system precision for paracetamol, cetirizine and phenylephrine was found to be 0.4, 0.3, 0.4. R_t for these three drugs were determined to be 0.710, 1.173 and 1.895 min since retention times are shortened, the approach created was valued.

1. Introduction

This is a brand new, sophisticated, advanced LC category that offers better chromatographic performance while maintaining the same fundamental idea and technique. and validate it according to ICH Q2(R1) guidelines. Since Effective cold remedies are highly sought after these days, particularly by those with hectic schedules who must focus and stay alert as soon as possible. Pharmaceutical companies were able to effectively accomplish this by adding more ingredients to their formulations in order to address several symptoms with a single pill or capsule. However, the examination of the increasingly complex dose forms presented several difficulties for quality control lab analysts, necessitating the growth of novel analytical procedures. It was crucial to take into account quick, easy, and inexpensive ways without sacrificing the precision and dependability of the outcomes. Numerous reliable techniques have been developed for using phenylephrine, cetirizine, and paracetamol either alone or in conjunction with other medications, according to a review of the literature. The

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purpose of this work is to create a stability-indicating reverse phase UPLC method and validate it according to ICH Q2(R1) guidelines. that will fill a research gap as it enhances the three parameters i.e. speed, resolution, and sensitivity [1].

Acetaminophen, is referred as paracetamol (N-(4-hydroxyphenyl)acetamide) is among the most widely used over-the-counter medications for reducing temperature and managing pain. It belongs to the drug classes that include analgesics (pain relievers) and antipyretics[2,6].

An antihistamine drug called cetirizine is frequently used to treat allergy-related symptoms like hives, hay fever, and allergic rhinitis. It functions by inhibiting the normal production of histamine, which is responsible for symptoms of allergies such as itching, runny nose, and watery eyes[3,5].

A typical decongestant drug i.e. phenylephrine hydrochloride which is mostly used to treat nasal congestion brought on by allergies, colds, or sinusitis. It belongs to the class sympathomimetic amines, which lessen nasal edema and congestion by constricting the blood vessels in the nasal passages[4,7].

The main uses of cetrizine + paracetamol + phenylephrine are to treat symptoms of allergies and the common cold, including fever, runny or blocked noses, sneezing, congestion, and discomfort.The drug's structures are shown in fig no 1.

2. Objectives

The purpose of this work is to create a stability-indicating reverse phase UPLC method and validate it according to ICH Q2(R1) guidelines. that will fill a research gap as it enhances the three parameters i.e. speed, resolution, and sensitivity.

3. Methods

BBD Approach for the UPLC Method Development[14]

Risk Assessment Studies is the initial phase of early pharmaceutical development according to BBD. The planning and execution of investigations in this study were done using the Box-Behnken type response surface design. A statistical technique called response surface methodology (RSM) strategy was used in methodically designing a series of experiments for the optimization of different parameters. BBD is used for optimizing the chromatographic conditions for analytical methods shown in table no 1.

Optimization:

BBD was employed in this investigation to optimize the chromatographic conditions. The software has made use of SAS Institute subsidiary JMP®pro 17.0.0. Retention duration and tailing factor were the two responses for each drug that were optimized, and in this experiment, three elements were taken into account: temperature, flow rate, and mobile phase composition. In the given collection of variables, seventeen trials have been carried out. Of these fifteen trials, factor interaction effects were present in twelve trials. The optimal values for the chosen responses are indicated in the table with an asterisk (*), and their degree of significance was $p<0.5$. displayed in a table. The generated response surface graph displays the interactions depending on selected responses (RT PARA, RT CTZ, RT PHY, TF PARA, TF CTZ, TF PHY) shown in fig no 2,3,4,5,6,7.

METHOD DEVELOPMENT OF RP-UPLC[10]

Preparation of Standard working solution(100% solution): 1 ml stock solution was pippete out in 10ml volumetric flask and mixed with CH_3OH and water. (2 ppm ctz, 4 ppm phy, and 130 ppm para).

Sample stock solution (50 ppm ctz, 100 ppm phy, and 3250 ppm para) and sample working solution was prepared (2 ppm of ctz, 4 ppm of phy and 130 ppm of para).

2.2.3 VALIDATION[11]:

By making standard injections of 130 ppm + 2 ppm + 4 ppm of ctz, phy and para, the system suitability parameters were ascertained and depicted in below table no 1.

Specificity[13]: Analyzing any deviation from the ideal process.

Optimized Method*:* Chromatographic conditions:

MP composition: Buffer (0.01N KH_2PO_4) and CH_3OH taken in the ratio 55:45A

Flow rate : 0.3 ml/min

Column : ACQUITY UPLC CSH C_{18} Column, 1.7 µm, 2.1 mm X 100 mm.

Detector wavelength : 275 nm

Column temp : 24°C

Injection vol : 5 µl

Duration of run **:** 6.0 min

Solvent : CH_3OH and H_2O (70:30).

Observation : All system appropriateness metrics, including tailing factor and plate count, were within acceptable boundaries, and the pharmaceuticals were satisfactorily eluted in terms of retention time and resolution.

paracetamol, cetirizine and phenylephrine were eluted at 0.710 min, 1.173 min and 1.195 min respectively with good resolution as depicted in fig no 9.

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Precision:
The precision was determined by preparing test solution of para, ctz and phy and were injected six times. Intermediate precision was determined and the data found was compared to standard limit.
Linearity[13]: Regression correlation coefficient method.

Standard stock solution was prepared.

25% Standard solution preparation: 3 standard stock solutions were pipetted out, yielding 0.25 ml each, similarly 50% , 75%, 100%, 125% and 150% standard solutions were prepared from standard stock sol I.

Accuracy: Standard addition method.

50%, 100% and 150% spiked solutions were prepared.

*Robustness:*Robustness is the ability of an analytical process to withstand slight intentional changes to its parameters.

LOD (Limit of detection): standard deviation slope method.

Sample Preparation: Three standard stock solutions, each containing 0.25 ml, were pipetted out into three separate 10 ml volumetric flasks and mixed with diluents to make up 0.3ml, 0.3ml, and 0.3ml of the para, ctz, and phy solutions, were transferred to a 10ml volumetric flask

LOQ (Limit of quantification): standard deviation slope method.

Sample Preparation: Three standard stock solutions, each containing 0.25 ml, were pipetted out into three separate 10 ml volumetric flasks and mixed with diluents to make up 0.9ml, 0.9ml, and 0.9ml of the para, ctz, and phy solutions were transferred to 10ml volumetric flask[11,13].

2.2.4 Study on deterioration[12]:

Oxidation: Add 1 ml of the stock solutions of phy, ctz, and para separately, 1 ml of 20% H_2O_2 was added and maintained at 60°C for 30 min. To perform an UPLC analysis, the final solution was diluted to yield 130µg/ml, 2µg/ml, and 4µg/ml of each component. 10 µl solutions were then injected and chromatograms were recorded.

Acid degradation studies: 1 ml of 2N HCl was mixed with 1 ml of the stock solutions of phy, ctz and para. Chromatograms were then recorded after the solution was handled in the same way as the oxidation process.

Alkali degradation studies: The same procedure was followed by mixing 1 ml of 2N NaOH with 1 ml of the stock solution of the same.

Dry Heat Degradation Studies:
The standard medication solution was heated in an oven for one hour at 105^0C in order to investigate dry heat degradation. To perform UPLC analysis, the resultant solution was diluted to obtain 130 µg/ml, 2 µg/ml, and 4 µg/ml of each component.

PhotoStability studies:
The photochemical stability of the drug solution was ascertained by subjecting 130µg/ml, 2µg/ml, and 4µg/ml solutions to UV light and keeping the beaker in a UV chamber for a day in a photo stability chamber.

Studies on Neutral Degradation:
Drug refluxing in H_2O for 6 hours at 60º was used for the study. The resulting solution was diluted to produce 130µg/ml, 2µg/ml, and 4µg/ml of each component in order to perform a UPLC analysis.
Acceptance Criteria: It should only deteriorate by a maximum of 15%.

4. Results

Method development: To formulate the procedure, various columns, buffers, mobile phase ratios, pH levels, etc were changed. After a number of attempts and an interference check, an optimal procedure was created.

Optimized Method:The chromatogram was been plotted in methodology of specificity. (shown in fig no.9)
System suitability parameters (SSP)*:* (shown in table no 2 and fig no.10)

Validation
Specificity: (shown in fig no.11)
Discussion**:** R_t of Para, Phy and Ctz were 0.707min, 1.186 min and 1.906 min respectively.
Linearity: (shown in table no 3 and fig no.12,13,14)
Discussion: Para (32.5-195µg/ml), ctz (0.5-3µg/ml) and phy (1-6 µg/ml) were injected in a Duplicate manner. Linearity equations obtained for para was y= 18109x+8212.5, ctz was y = 19458x +602.07 and of phy was y = 19316x + 797.53. (correlation coefficient= 0.999)
Precision : System precision (shown in table no 4 and fig no.16)
Discussion: Average area, standard deviation and % RSD were calculated for three drugs and obtained as 0.4%, 0.3% and 0.4% respectively for para, ctz and phy. Acceptance criteria was less than "2" hence the system precision was passed in this method.

Repeatability: (shown in table no 5 and fig no.17)

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Discussion: Average area, standard deviation and % RSD were calculated for three drugs and obtained as 1.1%, 0.4% and 0.2% respectively for para, ctz and phy.

Intermediate precision:(shown in table no 6 and fig no.18)

Discussion: The % RSD for the three drugs were computed and came out to be 0.9%, 0.5%, and 0.3%, for para, ctz, and phy.

Accuracy: (shown in table no 7 and fig no.19)

Discussion: Three levels of Accuracy sample were prepared by standard addition method. Triplicate injections were given for each level of accuracy and mean % Recovery was obtained as 100.40%, 100.35% and 100.12% for para, ctz and phy respectively.

Robustness: (shown in table no 8)

Discussion: Samples were injected in duplicate while maintaining robustness requirements(plus/minus),(MP= Mobile phase, FR= flow rate). All the system suitability parameters passed with little to no impact. %RSD was not over the upper bound.

Sensitivity: (shown in table no 9)

Study on deterioration:

Discussion: After the injected samples' assay was computed, It was discovered that every sample exceeded the deterioration thresholds.

Table 1: BBD summary of factors and responses

Sl no	Flow rate (ml/min)	Temp (^{0}C)	Mobile phase	R_t of PARA	R_t of CTZ	R_t of PHY	TF of PARA	TF of CTZ	TF of PHY
1	0.4	19	45	0.701	1.18	1.901	1.55	1.61	1.21
2	0.4	24	40	0.703	1.182	1.902	1.56	1.62	1.22
3	0.3	19	40	0.702	1.184	1.903	1.58	1.64	1.23
4	0.2	24	50	0.7	1.183	1.9	1.57	1.63	1.2
5	0.2	24	40	0.704	1.18	1.904	1.54	1.65	1.19
6	0.3*	24	45	0.706	1.19	1.91	1.61	1.67	1.24
7	0.4	29	45	0.709	1.2	1.918	1.53	1.64	1.18
8	0.3*	24	45	0.706	1.191	1.911	1.62	1.68	1.24
9	0.2	19	45	0.709	1.199	1.919	1.64	1.7	1.27
10	0.3	19	50	0.71	1.185	1.918	1.65	1.72	1.29
11	0.3	29	40	0.709	1.2	1.92	1.68	1.73	1.26
12	0.3	29	50	0.8	1.21	1.921	1.66	1.74	1.3
13	0.3*	24	45	0.707	1.191	1.91	1.6	1.68	1.25
14	0.2	29	45	0.81	1.22	1.922	1.68	1.7	1.26
15	0.4	24	50	0.708	1.23	1.923	1.69	1.75	1.2

(*- optimised conditions, Rt- retention time, TF-tailingfactor, PARA- paracetamol, CTZ- cetirizine, PHY- phenylephrine)

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Table 2 : SSP for Para, Ctz, Phy

S no	Para			Ctz			Phy		
	R_t (min)	TP	TF	R_t (min)	TP	TF	R_t (min)	TP	TF
1	0.706	6392	1.63	1.186	3236	1.67	1.906	4037	1.25
2	0.707	6368	1.60	1.191	3276	1.69	1.909	4081	1.24
3	0.707	6463	1.61	1.193	3283	1.67	1.91	4097	1.24
4	0.707	6368	1.61	1.194	3210	1.67	1.912	4006	1.25
5	0.707	6364	1.63	1.196	3224	1.66	1.914	4010	1.25
6	0.707	6368	1.61	1.198	3248	1.67	1.916	4061	1.25

Table 3: Linearity table for Para, Ctz and Phy.

Para		Ctz		Phy	
Conc (µg/mL)	**Peak area**	**Conc (µg/mL)**	**Peak area**	**Conc (µg/mL)**	**Peak area**
32.5	597809	0.5	9991	1	19555
65	1176000	1	20241	2	39606
97.5	1779060	1.5	29965	3	58761
130	2361205	2	39520	4	79009
162.5	2969535	2.5	49707	5	97526
195	3525055	3	58505	6	115965

Table 4: System precision data for para, ctz and phy

S. NO	Area of para	Area of ctz	Area of phy
1	2353657	39865	78464
2	2364544	39685	78464
3	2374654	39585	79364

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4	2376454	39656	78464
5	2364534	39576	78574
6	2354644	39657	78643
Mean	2364748	39671	78662
S.D	9595.3	104.6	351.7
%RSD	0.4	0.3	0.4

Table 6: Intermediate precision data for para, ctz and phy

S. NO	Area of para	Area of ctz	Area of phy
1	2325646	39754	78234
2	2354745	39575	78346
3	2368746	39546	78345
4	2318545	39265	78345
5	2367676	39746	78954
6	2364545	39476	78346
Mean	2349984	39560	78428
S.D	22273.1	182.6	261.4
%RSD	O.9	0.5	0.3

Table 5: Repeatability table of para, ctz and phy

S. NO	Area of para	Area of ctz	Area of phy
1	2346644	39457	78354
2	2346546	39667	78364
3	2368767	39456	78354
4	2307976	39675	78057
5	2326463	39746	78645
6	2374645	39857	78465
Mean	2345174	39643	78373
S.D	25151.6	159.7	191.4
%RSD	1.1	0.4	0.2

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Table 7: Accuracy information for para, ctz, phy

% Level	Spiked (µg/m)	RecoveredAmount (µg/mL)	% Recovery	Mean % Recovery
Para 100%	130	131.1	131.1	110.30%
	130	130.554	130.554	
	130	129.956	129.956	
Cet 100%	2	2.01	100.31	
	2	2	100.23	
	2	2.01	100.26	
Phy 100%	4	4	100.18	
	4	4	100.08	
	4	4	100.06	

Table 8 : Robustness data for para, ctz and phy

S.NO	Condition	%RSD of para	%RSD of ctz	%RSD of phy
1	FR(-) : 0.2ml/min	O.5	0.3	0.6
2	FR(+) : 0.4ml/min	0.3	0.9	0.4
3	MP (-): 50B:50O	0.1	0.3	0.4
4	MP (+): 60B:40O	0.4	0.3	0.9
5	Temperature(-): 19ºC	0.5	0.1	0.7
6	Temperature(+): 29ºC	0.5	0.3	0.6

Table 9: Sensitivity table of para, ctz and phy

Drug name	LOD(µg/ml)	LOQ(µg/ml)
para	1.26	3.83
ctz	0.07	0.21
phy	0.02	0.05

Table 10: Degradation Data of para, ctz, phy

S.NO	Degradation Condition	%Drug UnDegraded	%Drug Degraded	% Drug UnDegraded	% Drug Degraded	% Drug UnDegraded	% Drug Degraded
1	Acid	98.76	1.24	98.76	1.24	98.51	1.49
2	Alkali	99.10	0.90	99.84	0.16	98.37	1.63
3	Oxidation	93.27	6.73	94.58	5.42	94.95	5.05
4	Thermal	99.17	0.83	99.81	0.19	99.78	0.22
5	UV	99.47	0.53	99.59	0.41	99.65	0.35
6	Water	99.94	0.06	99.86	0.14	99.78	0.22

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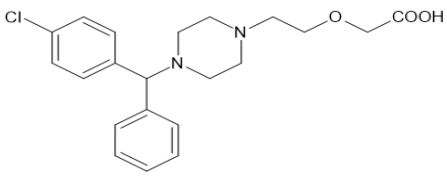


Fig 1a

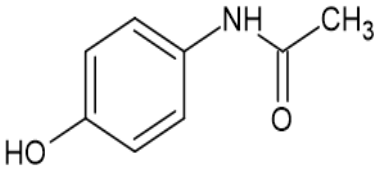


Fig 1b

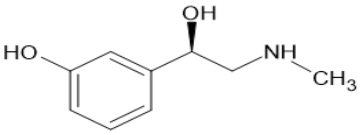
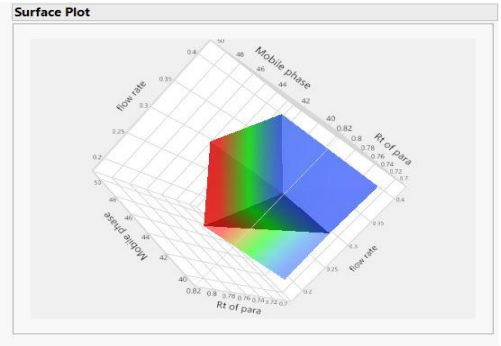


Fig 1c

Fig 1a, 1b, 1c : Structures of cetirizine, paracetamol and phenylephrine



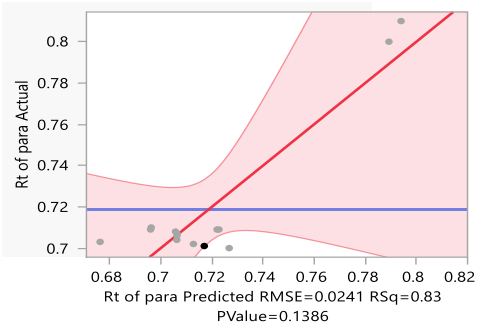
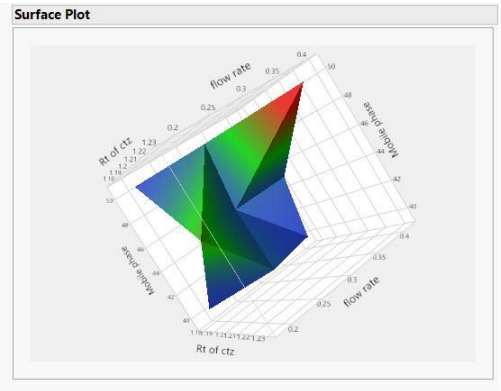


Fig 2. Response surface graph of R_t of PARA related to MP & FR (MP=Mobile phase, FR=Flow rate)



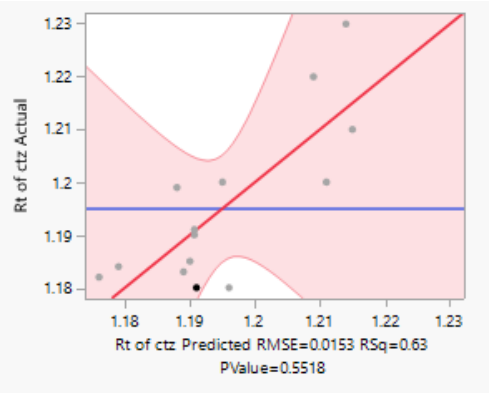
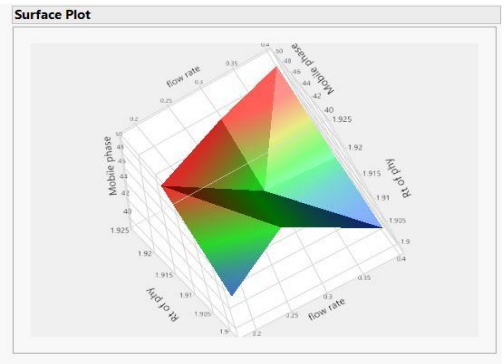


Fig 3. Response surface graph of R_t of CTZ related to MP & FR



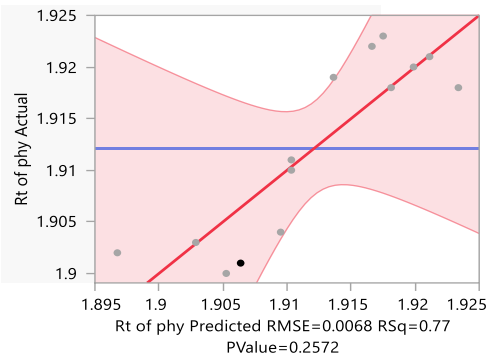


Fig 4. Response surface graph of R_t of PHY related to MP & FR

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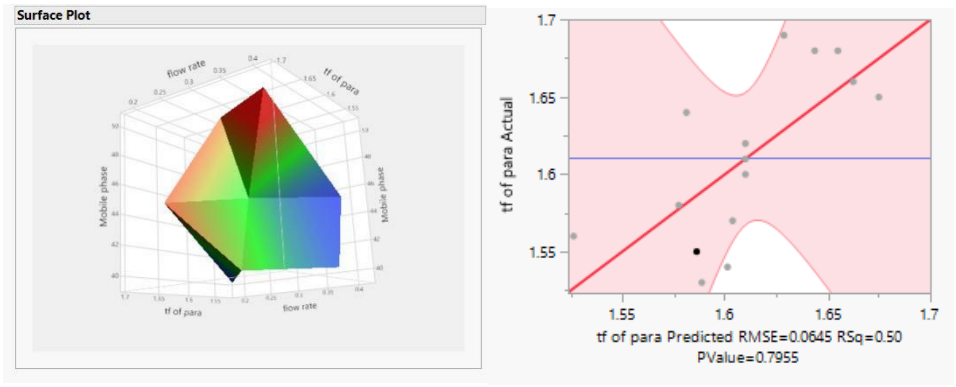

Fig 5. Response surface graph of TF of PARA related to MP & FR

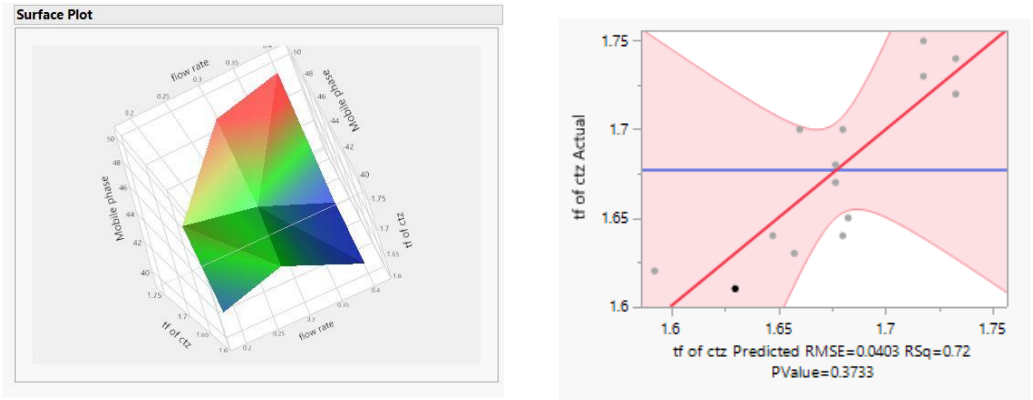

Fig 6. Response surface graph of TF of CTZ related to MP & FR

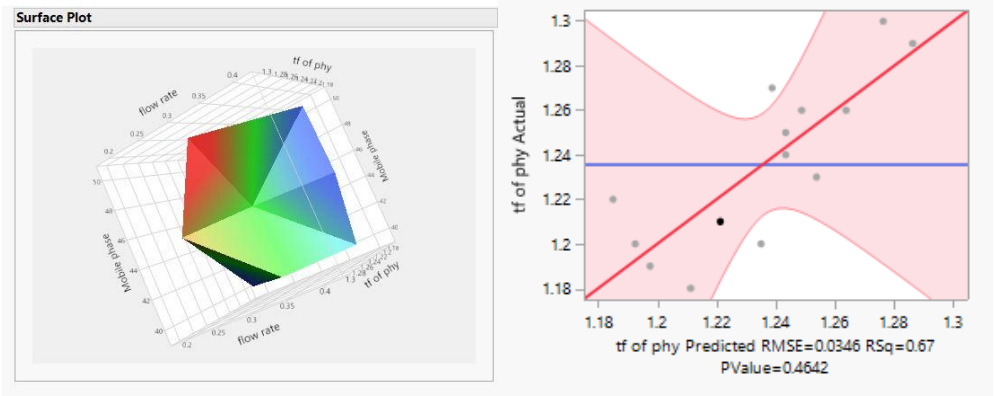

Fig 7. Response surface graph of TF of PHY related to MP & FR

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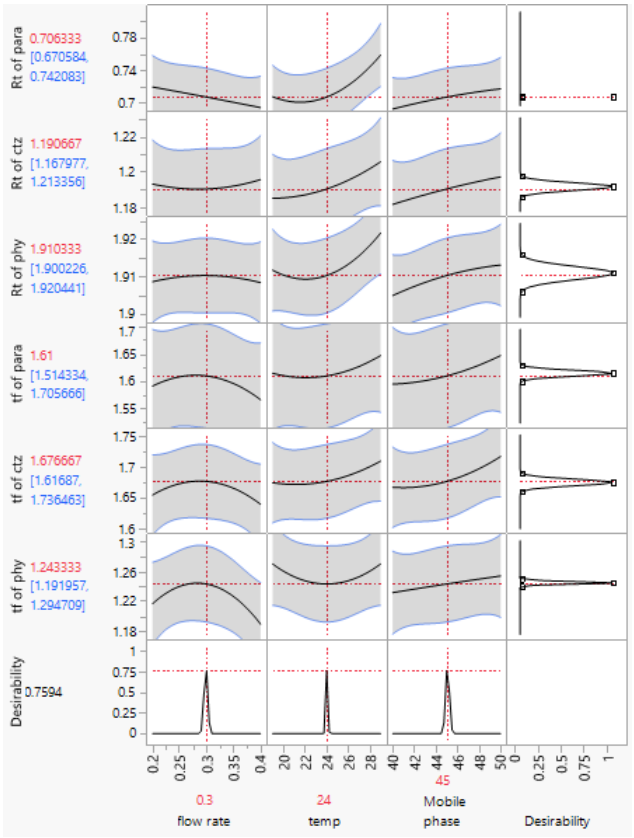

Fig 8. Prediction profile

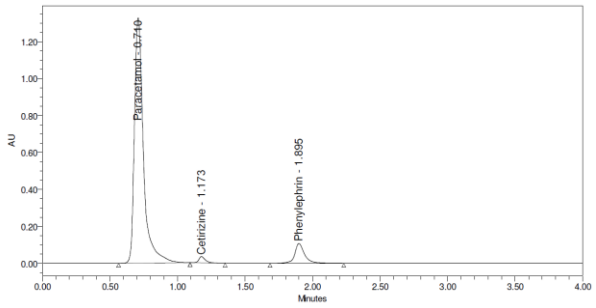

Fig 9. Chromatogram of optimized condition

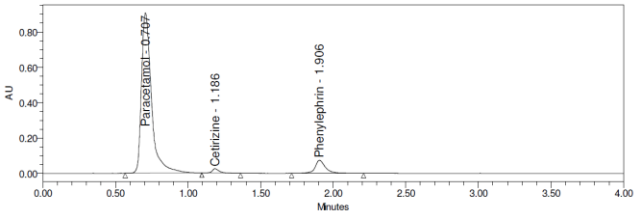

Fig 10. System suitability chromatogram

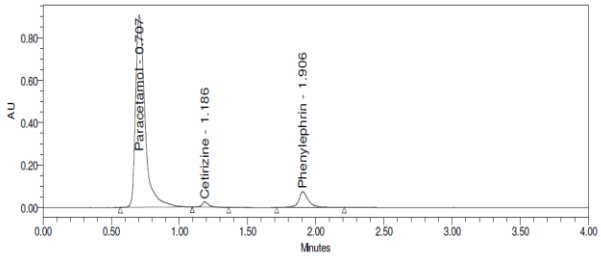

Fig 11. Selectivity chromatogram

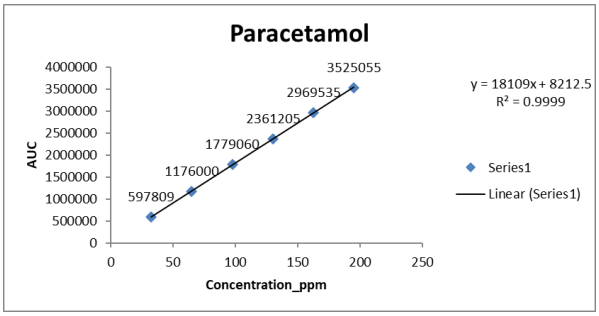

Fig 12. Calibration curve of Paracetamol

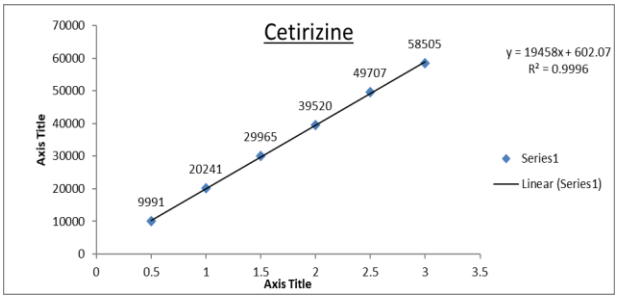

Fig 13. Calibration curve of Cetirizine

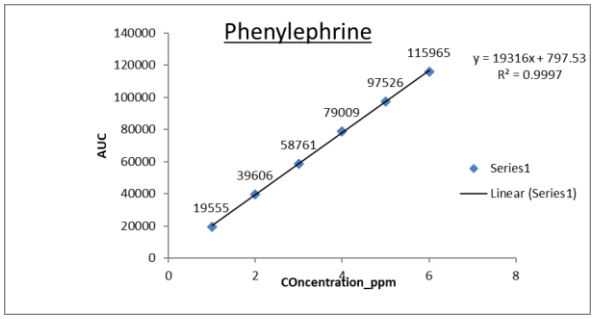

Fig 14. Calibration curve of Phenylephrine

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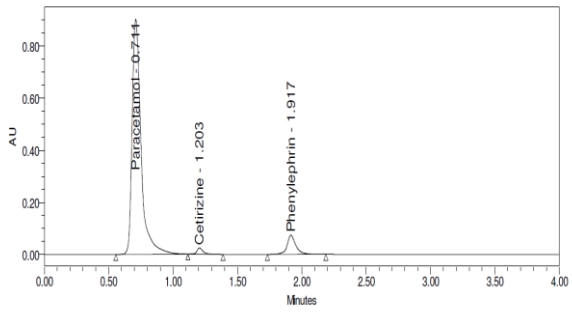

Fig 15. Linearity 100% Chromatogram

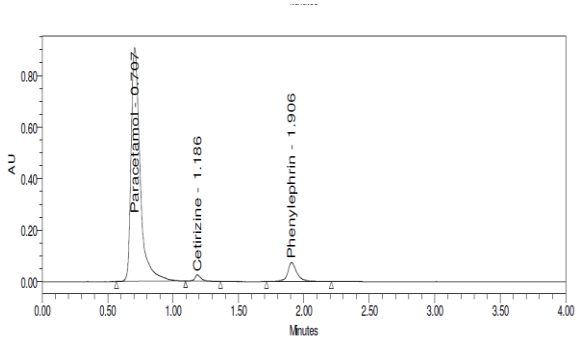

Fig 16. System precision chromatogram

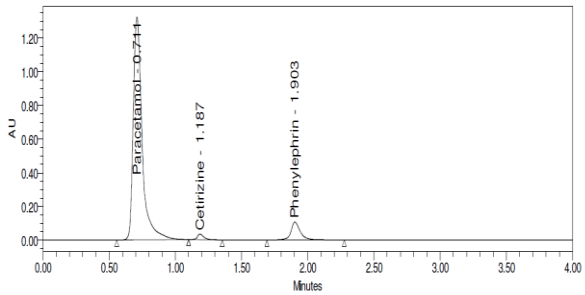

Fig 17. Repeatability chromatogram

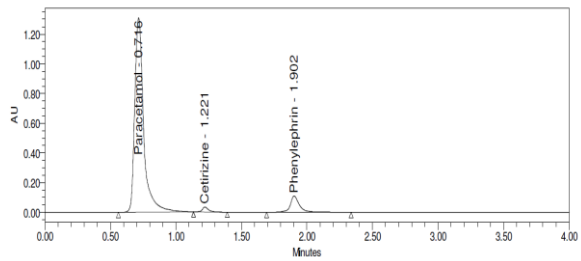

Fig 18. Intermediate precision chromatogram

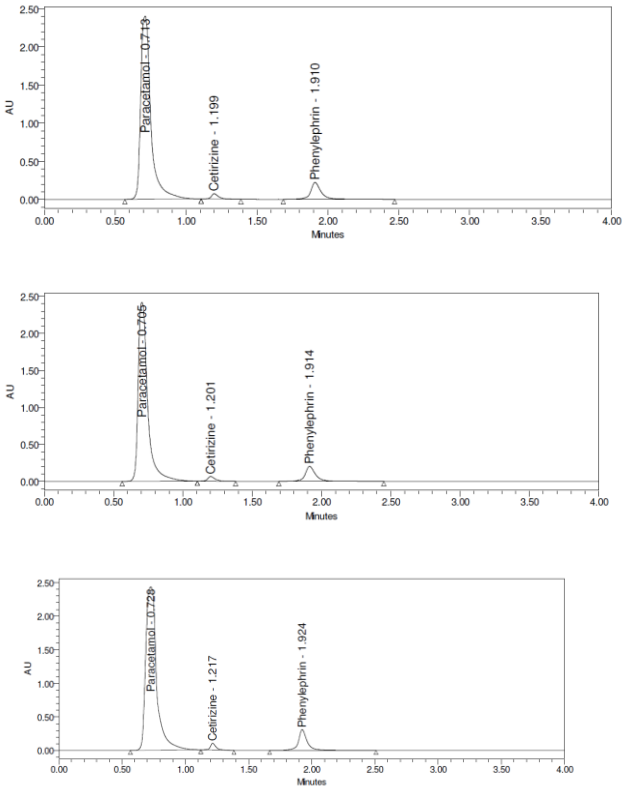

Fig 19. Accuracy 100% chromatogram

5. Conclusion

A simple, Accurate, precise method was developed for the simultaneous estimation of the paracetamol, cetirizine and phenylephrine in solid dosage form. The %RSD of system precision for paracetamol, cetirizine and phenylephrine was found to be 0.4, 0.3, 0.4 respectively. R_t for these three drugs were determined to be 0.710, 1.173 and 1.895 min. %RSD of method precision for paracetamol cetirizine and phenylephrine were and found to be 1.1, 0.4 and 0.2 . % recovery was found as 100.40%, 99.73%, and 100.12% for paracetamol, cetirizine and phenylephrine. The regression equations for paracetamol, cetirizine, and phenylephrine yielded LOD and LOQ values of 1.26 ppm, 0.07 ppm, 0.02 ppm, 3.83 ppm, and 0.21 ppm, 0.05 ppm, respectively. Regression equation of paracetamol was y = 18109x + 8212.5, cetirizine was y = 19458x + 602.07 and of phenylephrine was y = 19316x + 797.53. Because retention times are shortened, the approach created was valued.

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