RESEARCH ARTICLE

Utilization of Becalutamide Pertinent to Antiandrogen for Development and Validation - A New Perspective

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ABSTRACT

A new validated HPLC process is developed to determine Bicalutamide (BIC) in pharma formulation. For this analysis Hypersil ODS C18 100 mm × 4.0 mm, 3µ Column, or equivalent is used as a chromatographic column. Isocratic elution is observed at 1.00ml/min. Water as 70v/v, tetrahydrofuran as 20v/v, and acetonitrile as 10v/v of were used as a mobile phase. Run time was identified at 0.50mL/min to 1.50mL/min. 225nm is the UV detection wavelength. 4.0µl sample is injected into the column. For the Sample, blank, placebo, system suitability run time is measured at a time interval of 16 minutes, and for the diluted regular sample it is 60minutes. ± 2.4 minutes is the approximate retention time is identified to BIC. % R.S.D is calculated. For this drug mean percentage recovery is within the limit. By considering the values obtained, this prospective HPLC is successfully applied to formulations. The waste materials obtained in this process may associates with the environment without intervention, the problems ripple to both the ecosystems as well as communities, which may causes severe environmental and health risks. By considering the environmental concerns the waste products so obtained are subjected to Biological treatment (land farming) to control the hazardous waste if any, regated the both halogenated as well as non-halogenated solvents. This developed process is more simple also is exceptional to that of unalike mechanism which can be used in dose forms of syrup.

Keywords: RP-HPLC Refractive index detector, BIC, Rate of flow, USP reference.

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INTRODUCTION

The Molecular formulae for Bicalutamide (BIC) is $C_{18}H_{14}F_4N_2O_4S$. This drug associates with discriminatory blocking androgen receptor, biological target to androgen sex hormones testosterone along with di-hydro-testo-sterone.[1] Medication some estrogen-like possessions in adults whenever utilized as monotherapy because of enhanced levels of estradiol .[2-4] BIC is well-absorbed, also its absorption does not accouterments through food.[5] This may acts as a antiandrogen medication which is basically utilized for treating cancer named as prostate.[6] Bicalutamide provides elevated liver enzymes in around 1% of people.[7,8] The structure is represented in the figure 1. V.V.S.S. Raman Nanduri et.al.,[9] described total six related foreign substances named as Impurities-08, 09, 10, 12, 13, and 14 for BCT. Zorbax SB phenyl column (150 × 4.6mm × 3.5µm) along with HSS T3 column (100 × 2.10mm × 1.80µm) is used. QL are identified as 0.02% to 0.03 to both processes. Linearity to foreign impurities is in range of QL - 200% for specification level as well as correlation coefficients those are measured by respective calibration curves are nearly 0.999. Recoveries identified as 90 to 100%, 98 to 102%. Abhishek Arya et.al., [10] utilized Lichrocart CN column (250 × 4mm, 5µm, MERCK). Rt value for both hesperetin and bicalutamide is 2.80min., 4.28min. Wavelengths are 288nm, 270 nm. Intra-day as well as inter-day assay precision along with accuracy are identified as <2% on linearity range as 50ng/mL to 2000ng/mL. LOD, LOQ to both bicalutamide, hesperetin is 14.70ng/mL, 44.57ng/mL and 16.11ng/mL, 48.84ng/mL. A. R. Nageswara Rao et.al.,[11] described the recoveries at 99.68%–100.25% by <1% R.S.D. The LOD and LOQ are (2.4×10^{-8} g/ml, 3.0×10^{-8} g/ml and 7.6×10^{-8} g/ml, 9.3×10^{-8} g/ml to (*S*)-(+)-BCT as well as (*R*)-(−)-BCT enantiomers. Linearity is 10.00 µg/ml –250.00 µg/ml. M. van Nuland et.al.,[12] are done by triple quadrupole mass spectrometer operating in the positive and negative ion-mode. Assay ranges are 2.00ng/mL to 200ng/mL, 0.20ng/mL to 20.00ng/mL, 10.00ng/mL to 200.00ng/mL, 1.00ng/mL to 20.00ng/mL, 1.88ng/mL to 37.50ng/mL and 1500ng/mL to 30,000 ng/mL. Because of very less sensitivity, the end extract from samples of patient are strengthen before to injection as well as samples of QC to get adequate sensitivity. P. P. Sancheti et.al.,[13] observed the wavelength at 272 nm by absorptivity as 2.3399×10^3 /mol/cm. Strength range is 1.50µg/ml -

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Table 1: Outcome of System suitability

	Solution	BIC Outcome
Tailing factor	Bicalutamide	1.3
% RSD	Bicalutamide	0.3
Theoretical plates	Bicalutamide	6997
Resolution	System suitability	1.

18.00µg/ml. LOD and LOQ are 0.10µg/ml and 0.4 µg/ml. Proposed this method[14-16] on Waters Symmetry C18, (150mm x 4.6 mm) 3.5m particle size column using 0.1%v/v trifluoro acetic acid and 0.05%w/v sodium-1-octane sulphonic acid in water as 65v/v along with 0.1%v/v tri-fluoro-acetic acid taken in acetonitrile as 35v/v as mobile phase in isocratic elution mode. Analytes are measured with help of PDA detector which is set as 270nm along with rate of flow as 1.20mL/min. By using literature reviews authors are carried out this method to development of BIC and it's associated impurities in Tablets (OSD) formulations. Further developed method was validated as per ICHQ (2A) guidelines.[17]

MATERIALS AND METHODS

The required chemicals for this analysis like Bicalutamide - R, Bicalutamide - S and bical-sulfoxides (6) (having the purity about 99.9%) were purchased from Symed Labs Ltd. HPLC grade acetonitrile was procured from Merck Millipore India Ltd. From Billerica, USA Milli-Q water from Millipore water system was used in each and every stage of the experiment. Analytical grade Tetrahydrofuran, formic acid along with TBME (Tertiary Butyl methyl ether) was obtained from Sigma Aldrich (Hyderabad, India). From Hyderabad, India Blank plasma was purchased from visakhapatnam blood bank.

Experimental

Hypersil ODS C18 100mm × 4.6 mm, 3µ, or similar is utilized to analysis of chromatography. By provincial

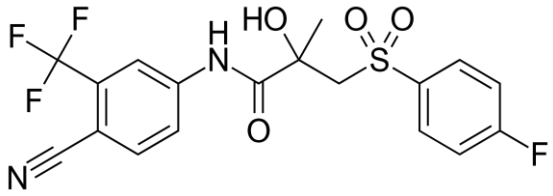


Figure 1: Structure of Bicalutamide

Table 2: Specificity results

Solution		Rt in min.
Blank as Diluent		---
Preparation of placebo		---
System Suitability solution	Bicalutamide	9.331
	Bicalutamide related compound B	10.274
Standard solution		9.351
Sample preparation		9.358
Bicalutamide amino benzonitrile		3.232
Bicalutamide related compound A (Isomer A and isomer B)		7.019
Desfluro Analog		7.086
2-fluro Isomer		7.878
Des hydroxy Analog		11.619
BIC-3 Standard		31.383
Spiked sample	Bicalutamide amino benzonitrile	3.229
	Bicalutamide related compound A (Isomer A and isomer B) and Des fluoro Bicalutamide	7.042
	2-fluro Isomer	7.906
	Des hydroxy analog	11.598
	Bicalutamide	9.329

market reference sample of BIC is procured. AR grade acetonitrile, and water are utilized for this experiment. Altogether 700v of water, 200v of Tetra-hydro-furan, also 100v of Acetonitrile are used for this analysis. Required quantity of BIC is taken about 8.20mg in 200.00mL standard flask with 100mL of analyte as well as marked to volume by advisable analyte. Finally, this total preparation allows 0.04 mg/mL BIC. Required quantity of BIC is taken about 8.2 mg, BIC related compound B is taken about 4.00mg in 100.00mL regular flask. This is subjected to dissolution by using 10.00mL of tetra-hydro-furan sonicated for dissolving. Latter it is marked to the volume using suitable analyte. Transferred the same by taking 5.00mL of this solution in to a 10.00mL regular flask. Again this is dissolved to volume by suitable analyte. Exactly 20 tablets are subjected to weighing after that bewildered to compose a powder amist mortar using the pestle. 50.00mg BIC powder sample is transferred in 100.00ml regular flask after that diluted by using 70.00mL of Tetra-hydro-furan. This flask is kept for sonication in a time interval of 20 minutes and kept for room temperature this suitable quantity by tetra-hydro-furan and attenuated

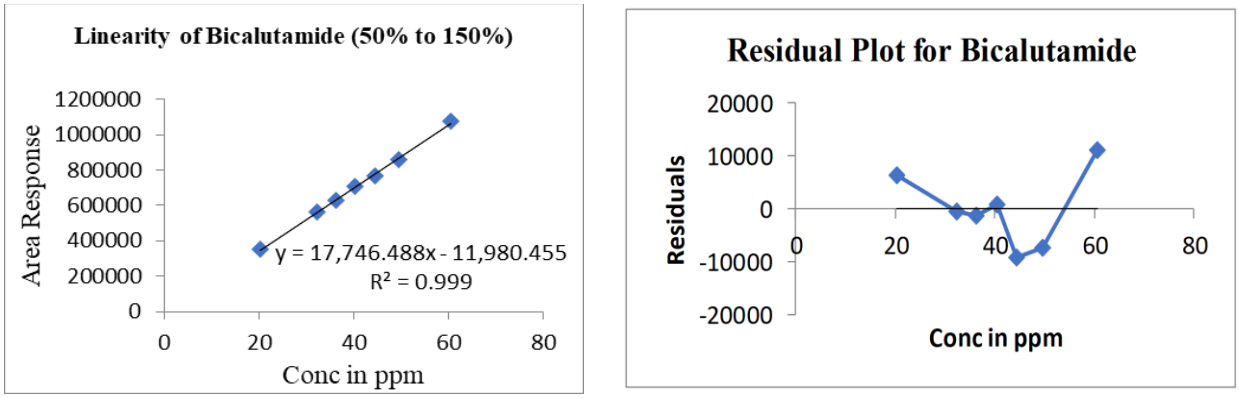


Figure 2: Linearity and residual plot for BIC

Table 3: Results for system precision (BIC)

Injection No.	Rt in min.	Area response
1	9.041	760462
2	9.014	766720
3	9.010	762239
4	8.997	763153
5	8.998	762824
6	8.995	765417
Mean	9.009	763469
%RSD	0.2	0.3

comprehensively. After that centrifugation is performed by using regular flask with 3000rpm in a time interval of 10 minutes. Transferred 4.00mL supernatant solution in a 50.00mL standard flask after that subjected to dissolution.

Optimization of Chromatographic Circumstances

Mobile Phase-A consists of a composition of 5v/v buffer solution, 35v/v acetonitrile, as well as water as 60v/v. Mobile Phase-B consists of pH 7.0 containing phosphate buffer as 5v/v, 45v/v acetonitrile, and 50v/v water. The rate of flow rate is identified as 1.20mL/min. Volume injected is 50.00µL. Temperature is nursed at 45°C where as sample temperature is nursed at 15°C. Wavelength detected at 265 nm. Run time was 50 minutes.

Method Development

By taking BIC as 40ppm solution UV spectrophotometer using methanol spectrum is taped solely. For the BIC, the peak wavelength is observed at 270nm. Obligatory estrangement along with peak expectations were identified over Hypersil ODS C18 100 mm × 4.0 mm, 3µ Column, or equivalent. Transferred 700.00mL of water, 200.00mL of Tetrahydrofuran and 100.00mL Acetonitrile in 1000.00 mL regular flask. Peak of chromatography is nearly freed to tailing also authorized which is suitable of all consolidations. Retention time is measured range of 0.50mL/min – 1.50mL/min. By the observations of reaction 1.5mL/min rate of flow is tolerable to effective separation of analyte.

Table 4: Comparison results of precision for Bicalutamide Tablet

Sample Set No.		% of Assay
Method precision	1	98.5
	2	97.6
	3	98.2
	4	98.5
	5	98.2
	6	97.4
Intermediate precision	7	95.1
	8	95.7
	9	94.9
	10	95.2
	11	95.4
	12	94.7
Mean		96.6
%RSD of 12 Determinations		1.6

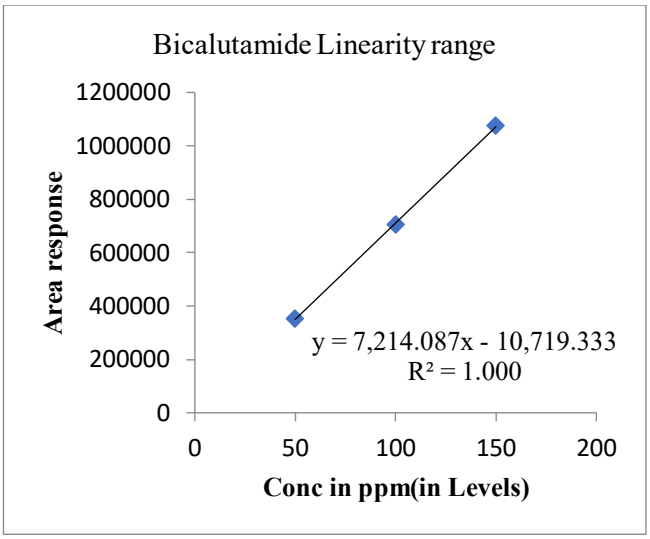
Table 5: Preparation of linearity ranges and Precision at Lower & higher ranges

	Linearity Regular Stock solution	Made up volume in mL (with diluent)	Lower Level	Higher Level
1	1.00	10	353785	1079456
2	1.60	10	352374	1069670
3	1.80	10	350632	1073355
4	2.00	10	353106	1074491
5	2.20	10	351943	1074435
6	2.45	10	353854	1072739
7	3.00	10	-	-
	Mean	-	352616	1074024
	%RSD	-	0.3	0.3

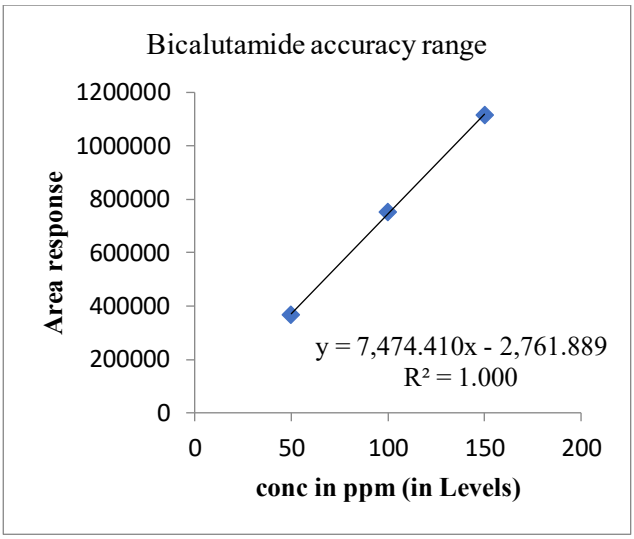
RESULTS AND DISCUSSION

System Suitability

Injected Blank as 1 injection, system suitability solution as 1 injection, 5 injections as regular solution into the chromatogram also recorded various chromatograms. By using listed below values, it is finished that this process is



Linearity range of BIC



BIC Accuracy range

Figure 3: Linearity range and Accuracy range

Table 6: Recovery ranges

Set	%Levels	Response in the area	Added as mg.	Actual Added as mg.	Recovered as mg.	Recovery as %	Mean % Recovery	% RSD
1	50	369085	25.13	25.0797	24.8092	98.9	98.3	0.6
2		367430	25.21	25.1596	24.6980	98.2		
3		365541	25.19	25.1396	24.5710	97.7		
1	100	742239	50.11	50.0098	49.8919	99.8	99.7	1.1
2		777732	51.95	51.8461	52.2777	100.8		
3		735706	50.25	50.1495	49.4528	98.6		
1	150	1118174	75.20	75.0496	75.1616	100.1	99.8	0.3
2		1109136	75.11	74.9598	74.5541	99.5		
3		1117069	75.38	75.2292	75.0873	99.8		
(% RSD for each level and 3x3 levels)						1.0		

highly relevant to validation of this process. Seized values were tabulated in table 1.

Specificity

This parameter is assessed by passing the solution of Blank, solution of placebo, solution of system suitability, solution of regular, BIC-amino benzonitrile, BIC related compound A, Desfluro Analog, 2-fluro Isomer, Des hydroxy Analog, BIC-3 Standard, solution of sample and solution of spiked into chromatogram and truthful different retention times.

From the results it is concluded that there is no interference because of various peaks obtained to placebo, diluent, Bicalutamide amino benzonitrile, BIC related compound A, Desfluro Analog, 2-fluro Isomer, Des hydroxy Analog, BIC-3 Standard are not obstructing BIC peak and each other. At last it is finalized that at the retention time peak of BIC there is no hindrance because of Placebo, diluent, BIC-amino benzonitrile, BIC- related compound A, Desfluro Analog, 2-fluro Isomer, Des hydroxy Analog, BIC-3 Standard, regular. Seized values were represented in the table 2.

Table 7: Range results

Level	3 sets of Linearity to Mean Area	3 sets of Accuracy to Mean Area
50%	352616	367352
100%	705428	751892
150%	1074024	1114793
Coefficient of correlation	1.000	1.000
Coefficient of regression	1.000	1.000
RSD	-	1.0%

Stressed Condition Studies are performed by using specificity by stressed circumstances, preparation of the

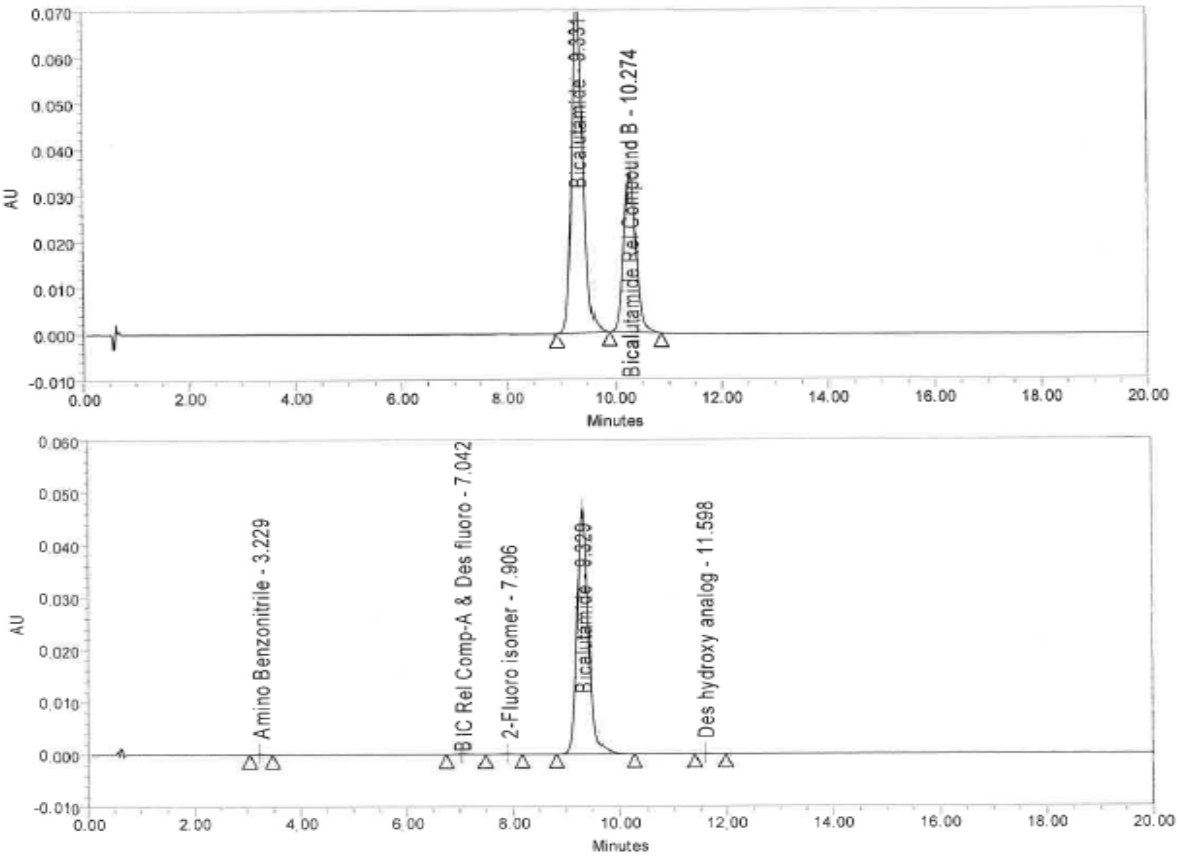


Figure 4: System suitability solution and Spiked sample

Table 8: Results for Spiked sample

No	Peak Name	Peak elution time	peak area µAU*sec	Purity angle	Purity threshold	Tailing	Plate count	results
1	Amino benzonitrile	3.229	1510	11.325	14.448	1.2	7020	Pure
2	BIC Rel compound A	7.042	2817	17.998	21.569	1.1	7444	Pure
3	2-Fluor isomer	7.906	2375	21.261	30.063	0.8	9099	Pure
4	BIC	9.329	695167	0.092	0.303	1.1	9830	Pure
5	Des hydroxy analog	11.598	1136	34.402	54.728	1.3	42392	Pure

Table 9: Robustness results

Evidence perception		USP Tailing factor	%RSD NMT	Resolution NLT	USP Theoretical plate Count
Original Condition		1.1	0.1	2.2	9094
Change in the flow rate	-0.2 ml/min	1.1	0.4	2.2	9238
	+0.2 ml/min	1.1	0.2	2.2	8560
Temperature	-5°C	1.1	0.3	2.4	9440
	+5°C	1.0	0.2	2.0	7858
Organic ratio	+2.0 %	1.1	0.2	2.3	9944
(Acetonitrile)	-2.0 %	1.4	0.3	1.7	5322
Organic ratio	+2.0 %	1.1	0.2	2.2	9833
(Tetrahydrofuran)	-2.0 %	1.1	0.2	2.3	10018
Wavelength	-5nm	1.1	0.2	2.2	9080
	+5nm	1.1	0.2	2.2	9067

sample, formation of placebo, 1.00N HCl, 1.00N NaOH, 3.0%w/v H_2O_2, stressed sample-neutral, which are exposed to UV light, sample which is exposed to Photo stability and sunlight, sample which is exposed to Thermal Stressed (Dry heat), sample which is exposed to Humidity, Alkali Stressed sample with 1.0N NaOH for 5 hour. At last, it is undergoes degrading in alkali within time interval of 4 hrs circumstances. Solutions like peroxide, neutral and acidic conditions BIC peak is marginally endures degradation.

Various unknown foreign substances, known foreign substances and divergent degradation foreign substances peaks are separated by peak of BIC. Therefore, assay process was measured as more specific as well as highly stability indicating.

System Precision

For this parameter % RSD for RT and response of peak for BIC from regular preparation are recorded. It is noticeable that from seized data RT as well as peak replies are same those are supported by RSD not more than to 1.0% and not less than to 2.0%. Because of this logic it is finished that precision of system reaches exactness of this process validation. It is finalized that the Rt, and response in the area are consistent which is finalized by relative regular deviation. Because of this sense, this parameter appease requirement to validation. Captured values were tabulated in Table 3.

Method Precision

This parameter is analogous sample for individual group is subjected to analysis to about 6 times. Provides information that this parameter is providing regular values for individual group or not. A calculated assay value to 6 determinations is 2.0.

Intermediate Precision

Analyzed the samples of BIC tablets for 6 reduplications by this procedure and calculated percentage assay of BIC. Calculated % of assay correlated values so achieved in this parameter as well as Intermediate Precision. For these two parameters determined the % RSD. %RSD calculated to assay for 6 convicted, and for reckoned is 2.0. At 12 hours of time interval, at 10°C the regular solution is durable and noted % discrepancy is 1.4. Sample Solutions is highly stable in a time interval of 22 hours at a temperature range as 10°C (% variation of 1.3). Obtained results are tabulated from Table 4.

Linearity

For this parameter, 50% and 150% linearity of BIC is measured with working strength also covered minimal 05 ranges as 80% - 120%. A graph is drawn after seeing PPM over X-axis, and area response over Y-axis. Precision at Lower as well as higher ranges for %RSD is 5.0. From statistical treatment of linearity data of BIC, straight among 50% range to 150% specification limit. Correlation as well as regression coefficient are 0.998. Residual shows that readings are generally dispersed incoherently to a value of zero, P-value is deliberated. P value is > 0.3. Intercept is ± 2% with response area at a rage as 100%. Results were denoted in table 5 and related linearity graph has given in figure 2.

Accuracy

Single and mean recovery to every spectrum lies in 50% - 150% for known foreign substances. Individual and mean recovery lies in 80.0% - 120.0% for BIC. Results for accuracy were tabulated in table 6.

Range

%RSD obtained for all accuracy range persistence is 2.0. Correlation as well as regression coefficient is 0.998 to Linearity also accuracy range parameter. Finally from the results obtained the method range is 50% - 150% of target strength for BIC. In the Fig. 3 and 4 linearity by accuracy

range graphs are represented. Linearity and accuracy range values are tabulated from Table 8.

Robustness

Changed the column temperature at a temperature range as 5°C. Total foreign substances are known, taken off each other by peak of BIC in sample spiked with foreign substances. It is finalized that this proposed process is more robust obliging cramped alterations possible in this process. Results tabulated in table 9.

CONCLUSION

Revised different parameters of RP-HPLC, distinct configurations for mobile phase were thoroughly noted and tested. A satisfactory segregation by good symmetry of peak is measured by configurations. For this anlaysis column used as Hypersil ODS C18 (100 × 4.6) mm, 3µ, or proportionate. Mobile phase is used as a 70v/v of water 20v/v of tetra-hydro-furan and 10v/v of acetonitrile. The better resolution is obtained at a rate of flow 1.50 mL/min when compared with other mixtures. Stressed circumstance the peaks of diluent, Placebo, BIC-amino benzonitrile, BIC- related compound A, Desfluro Analog, 2-fluro Isomer, Des hydroxy Analog, BIC-3 Standard may not interfere with BIC Peak and each other. There is no interference of Blank (diluent), Placebo, & known peaks of foreign substances by the peak of BIC. Angle for the purity is less to that of peak threshold by using empower software. If any degradation obliging are presented those are well separated from Peak of BIC. For, system suitability the tailing factor is 2.0 and theoretical plates are 2500. Peak tailing of BIC in regular injection is 2.0 by %RSD by 6 replicated injections of regular is 2.0. %RSD for Rt to peak of BIC is measured from total 6 injections of diluted solution is superlative to 1.0. %RSD area of BIC peak response deliberated to total 6 injections of regular solution (diluted) is 2.0. Assay (%RSD) of for 6 determinations is 0.5. %RSD for 12 measurements is 1.6. % variation in sample solution obtained among initial as well as specified period is 1.3 at a temperature range as 10 °C. As per the rules and regulations given by ICH, the HPLC process to related substance in product drug of BIC tablets is subjected to validation. Proposed process found as more specific. Method is also indicating as evidenced by stress circumstances. As per the rules and regulations by ICH as well as their requirements, this estimated HPLC process of associated compounds/substances in drug product named BIC has been verified. This proposed procedure has been measured to be specific. The approach is also shown by stressful circumstances.

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