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An Insight on Analytical Profile on Bisoprolol Fumarate – A Selective Beta-1 Adrenoreceptor Blocker

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Abstract BF is Beta-adreno receptor antagonist and used as an Anti-Hypertensive Drug. BF gives the blocking action on β1-adrenergic receptors in the heart and vascular smooth muscle. The present review compiles the various approaches implemented for quantification of BF in bulk drug, pharmaceutical matrix and biological fluid. This review represents more than 50 analytical methods which include capillary electrophoresis, HPLC, HPTLC, UV-Spectroscopy, UPLC, impurity profiling and electrochemical methods implemented for estimation of BF as a single component as well as in multicomponent.

Keyword: BF; Bioanalytical; UPLC/LC-MS; capillary electrophoresis; impurity profile

1. INTRODUCTION

BF is an extremely discriminatory β1-adrenergic blocker [1]. BF is chemically: (*RS*)-1-[4-[[2-(1- Methylethoxy) ethoxy] methyl] phenoxy] -3-[(1 methyl ethyl) amino] propan-2-ol fumarate **Figure 1**. It is official in, USP. BF has similar structure to metoprolol, bopindolol, hydrochlorothiazide, atenolol [2]. Structure of BF, there is two substituents at para position of benzene provide the activity of β-selectivity, In which it has two substituents in para position of benzene which might be the activity of β- selectivity [3]. White crystalline powder of BF was soluble in water, methanol, ethanol, and chloroform. [4]. BF blocks catecholamine stimulus of β1-adrenergic receptors in the heart (cardio-selective) and

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vascular smooth muscle, with decreasing the heart rate, cardiac output, systolic and diastolic blood pressure, and may be response orthostatic hypotension [5]. β-Blocker with calcium channel blocker mixture has efficacy in definite cardiovascular diseases like angina pectoris, myocardial infarction and hypertension [4]. For the decrease of workload on the heart and hence oxygen demands, so that the drug is pointed toward for secondary prevention of myocardial infarction, parallel therapy in patients with stable chronic heart failure, and for the treatment of hypertension and angina pectoris[5]. About 80% bioavailability given by BF after 10 mg oral dose[6]. The first pass metabolism of BF is about 20% and binding to serum proteins is approximately 30% [5]. The concentrations of plasma were taken in between 5 mg to 20 mg. It is contraindicated in person suffering from Psoriasis, Myasthenia Gravis, Sinus bradycardia, diabetes, depression and during Pregnancy. BF is available in combination with other drugs like HCT, AMD B, IRBE, CELI, METO T [7].

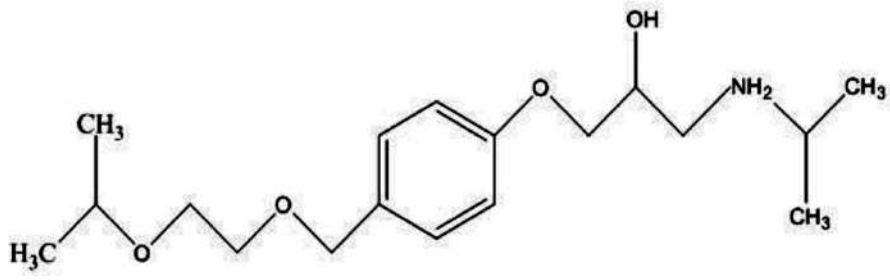


Figure 1: Chemical structure of BF.

2. ANALYTICAL ACCOUNTS ON BF

A variety of analytically urbanized methods like UV/Vis-Spectrophotometry, High-Performance Liquid Chromatography (HPLC), High-Performance Thin-Layer chromatography (HPTLC), Ultra Pressure Liquid Chromatography(UPLC), Liquid Chromatography-Mass Spectrometry (LC-MS), Capillary Electrophoresis and Stability indicating methods have been studied for analysis of BF. The present papers described consolidate analytical methods published so far estimation of BF in bulk and pharmaceutical formulation as well as in biological samples. In literature reported method describe the analysis of BF in various dosage forms as single components as well as in combination with HCT, AMD B, IRBE, CELI, METO T, tropaeolin and Bromocresol green. Summary of these methods for determination of BF is shown in **Figure 2**.

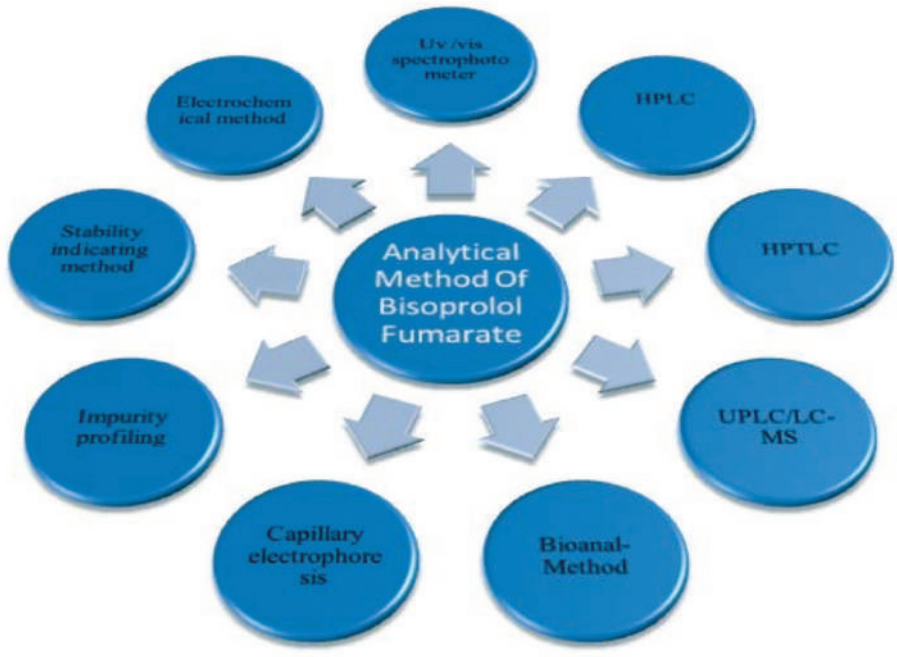


Figure 2: Analytical methods for BF.

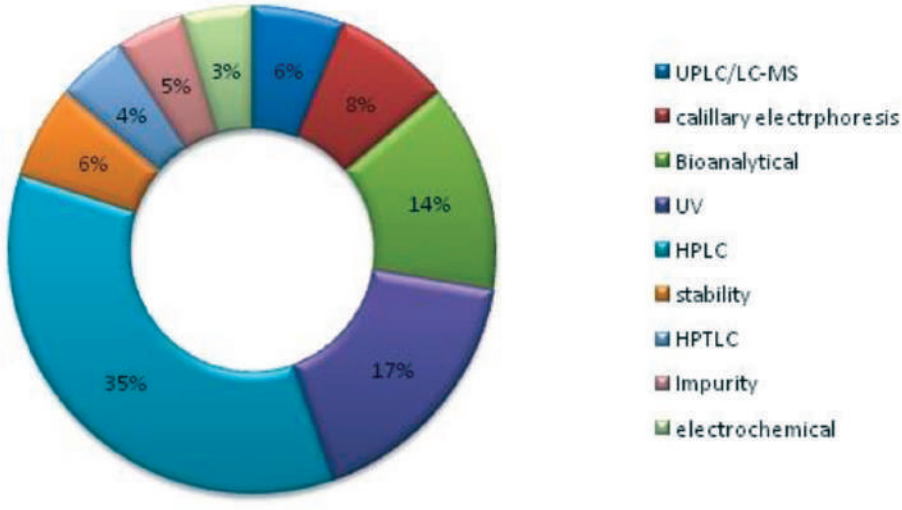


Figure 3: % Utility of analytical Techniques for BF.

3. PHARMACOPOEIAL STATUS

BF is the official drug in the (USP29) united state of pharmacopeia (2004). USP reported HPLC assay method using 4.6 mm × 12.5 cm column that contain packing L7 as a stationary phase and a mobile phase consist mixture of (65:35 % *v/v*). Water-acetonitrile used as diluents to 1 L portion add 5 mL heptaflurobutyric acid, 5 mL diethyl amine and 2.5 mL formic acid with flow rate 1 mL/min, the column outflow was scan at 273 nm [8].

Table 1: Dosage form, route of administration and recommended dose of BF.

Dosage forms	Dose	Route of administration	Indication / dose
Tablet	2.5 mg	Oral	Adult Hypertension 5 mg/day and maxim. 20 mg.
Tablet	1 mg		**Patients with renal impairment:** Not exceed 10 mg once daily.
Tablet	5 mg 10 mg		**Patients with severe liver impairment:** No dosage adjustment is required, however careful monitoring is advised.
Tablet	20 mg		The maximum recommended dose is 10 mg once daily. **Elderly:** No dosage adjustment is normally required. It is recommended to start with the lowest possible dose. **Children:** There is no experience with bisoprolol in children, therefore its use cannot be recommended for children.

4. UV/VIS-SPECTROPHOTOMETRIC METHODS OF BF [9 -20]

In article about nine UV-Spectrophotometric methods have been fixed for assurance of BFsingle and in combination of different dosage form. Also one spectroflurometric method has been accounted for determination of BF. The detailed summary spectrophotometer and spectroflurometer designating the basic principle, sample matrix, linearity and retention time in **Table 2.**

Table 2: Spectrophotometric methods used for determination of BF alone and in combined dosage form.

Sr. No	Drugs	Methods	Detection (nm)	Linearity (µg/mL)	Correlation coefficient (r^2)	LOD and LOQ (µg/mL)	Ref.
1	BIS with bromocresol green	Zero order	402	7 - 80	0.9998	LOD- 1.78 LOQ- 5.41	9
2	BF and HCT	First order	223 & 274	BIS 8 - 96 & HCT 4 - 48	0.999 & 0.998	_	10
3	BF	Zero order	412	5 - 30	0.9997	LOD- 0.67 LOQ- 2.23	11
4	BIS using methyl orange	Zero order	427	0.8 - 9	0.9997	LOD- 0.20 LOQ- 0.66	12
5	AMD B and BF	Zero order	356 & 270	2 - 18 & 10-100	0.9966 & 0.9941	LOD- 0.4854 LOQ- 0.2013	13
6	BF by using tropaeolin 00	Zero order	412	5 - 30	0.9995	LOD- 0.67 LOQ- 2.23	14
7	BF	Zero order	532 and 626	100 - 500 & 50 - 300	0.999 and 0.998	_	15
8	IRB and BHF	Zero order	476 and 479 IRB and BHF	20 - 90 and 40 - 160	0.9998 and 0.9998	LOD- 1.37 and 3.98 and LOQ- 4.17 and 12.06	16
9	BF and HCT	First order	BF 285.5 & HCT 264.5	1.2 - 59	0.9997 & 0.9998	LOD- 0.27, LOQ- 0.89 and LOD- 0.26, LOQ- 0.85	17
10	BF with BPB and BCP	First order	BF 402	In BPB 1.0–9.0 and in BCP 1.0–11.0	In BPB for BIS 0.9976 and BCP for BIS 0.9999	LOD in BPB and in BCP for BIS 0.1791 and 0.5868, and LOQ in BPB and in BCP 0.5964 and 1.9542	18

Sr. No	Drugs	Methods	Detection (nm)	Linearity (µg/mL)	Correlation coefficient (r^2)	LOD and LOQ (µg/mL)	Ref.
11	BF and PRH	Zero order	For both 610	2.0–16 and 2.0–18	0.9998 and 0.9989	LOD- 0.0678; LOQ- 0.2257 and LOD- 0.0678; LOQ-0.2257	19
12	BF and HCT	Zero order	224 and 273	3 – 21 and 3 - 18	0.9997 and 0.9999	_	20

5. SPECTROFLUROMETRIC METHOD OF BF

Hashem et al. (2016) reported IRB and BHF through spectroflurometric method. It is depend on charge transfer reaction between the designed drugs and 7-Chloro-4-nitrobenzen-2-oxa-1; 3-diazole NBD-CI. Dilution was prepared by using specific volume of NBD-CI (0.1%, *w/v*).By using 5 mL with acetonitrile it get heated and after cooling the fusion of solution was attenuate to 10 mL with acetonitrile and methanol for IRB and BHF, respectively. The absorbance was recorded at 476 and 479 for IRB and BHF, at colored concentration respectively against the reagent blank treated similarly. The linearity was obeyed in the range of 2.5–8 µg/mL for IRB and 6–16 µg/mL for BHF. This method also gives detection limits of 0.18 and 0.39µg/mL and a secondary quantification limit of 0.55 and 1.17µg/mL for IRB and BHF. The statistical evaluation of the results with the results of reported methods reflected that there was no major differentiation [16].

6. CHROMATOGRAPHIC SYNOPSIS

6.1 High-Performance Liquid-Chromatography [21-42]

Distant from Pharmacopoeial methods many HPLC methods were accounted for assurance for BF in pharmaceutical formulation. The outlined of expressed HPLC methods specifically the mobile phase used for estimation, columns, wavelength, correlation coefficient and linearity range is shown in the **Table 3**.

Table 3: HPLC methods of analysis for BF.

Sr. No	Name of drug	Columns	Mobile phase system	Discussion	Ref
1.	BF and HCT (tablet)	Inertsil ODS 3V	0.1 M potassium dihydrogen phosphate buffer and acetonitrile in the ratio of (70:30 % *v/v*)	Detection of BF and HCT was carried out at 228 nm and linearity obeyed in the range of 2.5–50 µg/mL and 6.25–125µg/mL. Retention time for BF and HCT was found to be 5.058 min and 2.783 min.	21

Sr. No	Name of drug	Columns	Mobile phase system	Discussion	Ref
2.	BF and HCT (tablet)	RP Zorbax Eclipse XDB-C18	Acetonitrile–water (25:75 % *v/v*) Containing 15mM phosphoric acid	Detection of BF and HCT was carried out at 225nm. Linearity range for BF and HCT 0.50–12.00 and 0.20–8.00 μg/mL Correlation coefficient for BF and HCT 0.999 and 0.999. Retention time for BF and HCT 5.058 min and 2.783 min.	22
3.	BF and AMD (tablet)	Luna C18-2	25 mM ammonium acetate adjusted to pH 5.0 and methanol (65:35 % *v/v*)	Detection of BF and AMD was carried out at 230 nm. Linearity was established in the range of 8–33 μg/mL. Retention time was 1.45 min and 3.91 min for BF and AMD. Correlation Coefficient for BIS 0.999 and AMD 0.999.	23
4	BF (tablet)	Hypersil ODS	mixture of buffer and acetonitrile in the ratio of (700:300 % *v/v*)	Detection of BF was carried out at 208nm. Retention time of 3.146 min. Linearity 5.00 - 17.5 µg/mL for BF. Correlation Coefficient 0.998.	24
5.	BIS F (tablet)	prontosil, chromo bond	buffer (pH 5.6) and acetonitrile in the ratio of (750:250 % *v/v)*	Detection of BIS F was carried out at 226nm. Linearity at 6 different levels from 25 μg/mL to 100 μg/mL. The retention time of BIS F was found to be 9.15min. Correlation coefficient 0.999917.	25
6.	BIS F and AMD B (tablet)	C18Intersil	Methanol: Acetonitrile: 50mM Potassium dihydrogen phosphate buffer KH2PO4 (25:30:45% *v/v*)	Detection of BIS F and AMD B was carried out at 267nm. Correlation Coefficient For BIS 0.998 and AMD besylate 0.999.	26
7.	BF and HCT (tab)	C18 column Kromasil 100-5C18 column	acetonitrile-0.01 M KH2PO4 (40:60% *v/v* and pH 3.5)	Detection of BF and HCT was carried out at 232nm. Linearity: - 1-7 and 2.5-17.5μg/mL for BF and HCT. Amplitudes at 228.4 and 283nm of BF and HCT. Correlation Coefficient For BF 0.9999 and for HCT 0.9999. Retention Time:- BF and HCT were eluted at 3.38±0.04 and 4.03±0.02 min.	27

Sr. No	Name of drug	Columns	Mobile phase system	Discussion	Ref
8.	BF enantiomer	Chiralcel OD column	methanolglacial acetic acid-triethylamine, (100:0.020:0.025% *v/v/v*)	Detection of BF was carried out at excitation/emission 275/305 nm. Linearity was found to be 5 - 250 ng/mL. Correlation coefficient of 0.999.	28
9.	BF and HCT (tablet)	C18 column Kromasil	Acetonitrile and phosphate buffer (40:60 % *v/v*, pH 3)	Detection of BF and HCT was carried out at 228. For both BF and HCT linearity was found to be 20-100 μg/mL.The retention time of BF and HCT were 3.3 min and 6.25 min. correlation coefficient 0.998 and 0.999.	29
10.	BF	C18 column Kromasil 100-5C18	Phosphate buffer (pH 3.5) and acetonitrile (70:30 % *v/v*) 1ml/min	Detection of BF was carried out at 225 nm. Linearity is 5-90μg/mL. Retention time 1.158 min.Correlation coefficient 0.9998 and regression coefficient 0.9996.	30
11.	BF (tablet)	Eclipse XDB C18	Water / methanol / acetonitrile in a ratio of (50:30:20 % *v/v/v)*	Detection of BF was carried out at 225nm. Two areas of linearity in the range of 0.8 - 80 g/ mL and 80 - 1000 g/ ML. Correlation coefficient 0.999 and intercept 0.4953 with a regression coefficient R2 = 0.999. LOD = 1.3 g/mL LOQ = 3.98 g/mL.	31
12.	BF and HCT and impurities (tablet)	BDS Hypersil C8 column	[acetonitrile-ammonium dihydrogen phosphate/ orthophosphoric acid buffer solution (80:20% *v/v)*	Detection of BF and HCT was carried out at 220nm. Linearity 1.50–46.20and 3.80–114.00 μg/mL. Correlation coefficient 0.9998 and 0.9998. Recovery: 98–102 % for active ingredients (B for HCT), 90–110 % for impurities (A, L, K For BF impurity).	32
13.	BF with potential impurity	LiChrosorb RP-18	Acetonitrile- 0.050 M ammonium phosphate buffer (4:6 % *v/v*).	Detection of BF and HCT was carried out at 226nm. Linearity: - 1 to 10 μg/mL. Regression coefficient of the linearity test was 0.9996.	33

Sr. No	Name of drug	Columns	Mobile phase system	Discussion	Ref
14.	BF with HCT	Zodiacsil-C18	buffer solution (pH 3.60) containing 5 mM monobasic potassium phosphate in milliQ-water. Mobile phase B consists of a mixture of acetonitrile and methanol in the ratio (80:20 % *v/v)*	Detection of BF and HCT was carried out at 226nm. Correlation coefficient obtained was 0.999. Stability indicating in the range of LOQ to 150%.The retention times was studied between ± 0.2 units.	34
15.	BF separated by chiral stationary column	Chiralpak IB	n-hexane/ethanol 95/5 % *v/v),* 0.2% DEA)	Detection of BIS was carried out at 223nm. Correlation Coefficient was found to be 0.8635. Retention Time was over 100 min.	35
16.	BF with selected excepient	Hypersil BDS C18	acetonitrile—potassium dihydrogen phosphate buffer (pH 3.0, adjusted with orthophosphoric acid; 20 mM) (50:50% *v/v)*	Detection of BF was carried out at 222nm. Linearity in the range of 10–100 μg/mL.Correlation Coefficient:-0.999. LOD and LOQ values were found to be 0.03 and 0.1g/mL. Retention Time:-4.00 min.	36
17.	BF Tab	Chromolith RP18-e	phosphate buffer (pH3.5): acetonitrile (77.5: 22.5 % *v/v)*	Detection of BF was carried out at excitation/emission 232/320 nm. Linearity range is 3 to 200 ng/mL, correlation coefficient of 0.9998 The LOQ was 3 ng/mL. Retention Time was detected 4.5min and 7.24 min.	37
18.	BF	Zorbax SB-C18 Solvent Saver Plus	0.1% formic acid solution – acetonitrile (50-50 % *v/v)*	Detection of BF was carried out at 226 nm. Linearity in the range of 1 ng/Ml and 100 ng/mL. Correlation Coefficient of 0.998599, LOQ is 1 ng/mL. Retention Time is 1.7 min and 1.9 min.	38
19.	BF	Kromasil C18 column	methanol and 0.05% phosphoric acid (40:60% *v/v)*	Detection of BF was carried out at exci. /emmi 275/305 nm. Linearity in the range of 10–100 ng/mL. Correlation Coefficient: - 0.994. LOD: 3 ng/ mL. LOQ: 10 ng /mL.	39

Sr. No	Name of drug	Columns	Mobile phase system	Discussion	Ref
20.	BF film coated tab	Nucleosil 100-5 C18 HD	water and formic acid as solvent A in the ratio (99% : 1% (v/v) and acetonitrile and formic acid as solvent B in the ratio (99% : 1% *v/v)*	Detection of BF was carried out at 225nm. The retention times are 16.2 min.	40
21.	BF and HCT	YMC Pack Pro C18 column	0.1% orthophosphoric acid and acetonitrile (55:45% *v/v)*	Detection of BF and HCT was carried out at 259nm. Linearity range of 40-120 µg/mL (BF) and 50-150 µg/mL (HCT). Correlation Coefficient :- 0.9999 LOQ was 0.398 and 0.385 µg/mL for BIS and HCT. LOD (µg/ml) 0.398 and 0.385.	41
22.	BF and HCT	Zodiac C18	phosphate buffer and acetonitrile in the ratio of (80:20 % v/v)	Detection of BF and HCT was carried out at 208nm. Linearity was obeyed in the range 2.5-75µg/ml and 3-90µg/ml of BF and HCT. The retention time of BF and HCT was found to be 2.253 min and 4.425 min. LOD and LOQ for BF 2µg/ml and 6µg/ml and for HCT 0.9 µg/ml and 1.8 µg/mL.	42

6.2 High- Performance -Thin- Layer Chromatography [43-45]

About 3 HPTLC methods have been studied for simulation determination of BF with HCT and camphorsulphonic acid in different pharmaceutical dosage form.

Emanual M Patelia et al. (2013) investigated specific and precise method for quantitative estimation of BFand HCT in pharmaceutical dosage form. The separation of the BF and HCT was conceded on aluminum plate precoated with silica gel $60F_{254}$using mobile phase chloroform: ethanol: glacial acetic acid (5:1.5:0.2 *v/v/v*).The R*f* value was found to be 0.62 and 0.40 for BF and HCT, respectively when the densitometry quantification was performed maximum at 225 nm. For analysis of BF and HCT, linearity was studied in the range of 200 - 1200 ng/band and 100 - 800 ng/band, respectively. Accurateness of the method was studied by % recovery and found to be 100.02 ± 1.14% for BF and 99.91 ± 0.96% for HCT [43]. Similarly; *Rao et al.* (2013) also developed and validated an

effortlessmanner for determination of BF and HCT. The separation was achieved on aluminum plates percolated silica gel 60 F_{254} using mixture of ethyl acetate: methanol: ammonia 10:0.5:0.5 v*/v/v)* as mobile phase with R*f* of BF and HCT were 0.60 and 0.38, in that order and detection was monitored at 225 nm. For estimation of drugs, the linearity experiment was performed in the range of 150-900 ng/spot for BF and 100-600 ng/spot for HCT. Linear regression for BF and HCT was 0.999 [44]. The established methods were validated for correctness, robustness and specificity as per ICH guidelines.

Patel et al. (2011) reported an enantiomer separation of BF by TLC and HPTLC by means of (+)-10-camphorsulphonic acid as a chiral selector. Chromatographic separation of BF was performed with optically pure (+)-10-camphorsulphonic acid as a chiral selector. The mobile phase set for separation was triethyl amine–methanol–1-pentanol (0.14:9.9:0.18, *%v/v/v*). For TLC detection was executed at UV-chamber at short wavelength 254 nm and for HPTLC densitometry detection performed at 224 nm. The calibration ranges for both the isomers were 5-30 μg/mL [45].

7. STABILITY- INDICATING METHODS (SIM) FOR ESTIMATION OF BF [46-51]

With reference four stability indicating methods studied accordingly for persistence of BF in bulk substance and pharmaceutical dosage form implementing several analytical techniques. The reported stability indicating methods for BF illustrating dosage form, column, mobile phase and linearity and retention factor presented in [**Table: 4**].

Table 4: Stability indicating methods of BF by HPLC and UPLC.

Sr. No	Drugs	Formulation	Column	Mobile Phase System	Detection	Discussion	Ref
1	BF	Tablet	Chromo band C18	Buffer/ Acetonitrile (75:25% *v/v*, pH 5.6)	226 nm	Linearity was found to be 25 and 100 μg/mL. Correlation Coefficient: - 0.9998. Retention Time:- 9.5	46
2	BF and AMD	Aq.solution	C18	Acetonitrile–water solution of 10 mM ammonium acetate (92:8 % *v/v)*	230 nm	Retention Time is 4.042 min.	47

Sr. No	Drugs	Formulation	Column	Mobile Phase System	Detection	Discussion	Ref
3	BF and HCT	Tablet	YMC Pack Pro C18	0.1% Orthophosphoric acid and acetonitrile (55:45 % *v/v)*	259 nm	Linearity for both BF and HCT: - 40-120 and 50-150 µg/mL .Correlation Coefficient was found to be 0.9999. Retention Times 3.688 min and 5.824 min.	48
4	BF	Tablet	HP1200	Acetonitrile-water solution (10 mM ammonium-acetate, pH 4.0, adjusted with concentrated acetic acid) at a ratio of (92:8 % *v/v*)	230 nm	R-value for zero-order reaction had the highest value 0.9747.	49
5	BF and HCT	Tablet	ACQUITY BEH C18	Mobile phase A consisting of a buffer solution (pH 3.60) containing 5 mM monobasic potassium phosphate in milliQ-water. Mobile phase B consists of a mixture of acetonitrile and methanol in the ratio 80:20 % *v/v*)	226 nm	Correlation Coefficient was found to be 0.999. A retention time was studied between ± 0.2 units.	50
6	BF and HCT	Tablet	Acquity UPLC BEH C18	Water : acetonitrile (50:50 % *v/v*)	225 nm	Linearity in the range of 0.5– 250 µg /mL for BF and 0.5–150µg/mL. Correlation Coefficient (r) was found to be 0.999. For human urine linear in the range between 0.5 and 10 µg / mL for HCT and 0.5–30 µg/ mL for BF. LOD and LOQ 0.07– 0.21 µg/ mL ; and 0.01–0.03 µg/ mL for BF and HCT	51

8. CAPILLARY ZONE ELECTROPHORESIS METHOD [52-55]

Laszlo Gagyi et al. (2006) established a effortless capillary electrophoresis method for estimation of various stereoselective β1-blockers and H1-antihistamines by human serum transferrin. For the chiral separation of stereoselective β1-blockers and H1- antihistamines, pseudostationary protein zone was used. In that developed method about 15 compounds were screened and nearly all of them illustrate longer migration time, showed a communication with transferrin. Stereoselective interaction was observed only for five β1-blockers(CEL, TALINO, MEPIN, BOPIN, and OXPRE) and for one H1-antihistamine (bromopheniramine). A polyacrylamide-coated (3%, noncross-linked)capillary (34 cm effective length 650 mm id) was carried out[52].

Hong-Bing Duanetal. (2015) described a new routine estimation of METO TandBF. In that developed method, capillary electrophoresis fixed with tris (2, 2'-bipyridyl)-ruthenium (II) electrochemiluminescence for the estimationas well asillustrates relationship between the METO T and BF and human serum albumin. There are different parameters were selected for optimization of CZE separation; because they affect the CZE separation and ECL detection, the optimized parameters like pH, amount of running buffer, detachment voltage and potential exposures. Under enhanced condition METO T and BF were well separated and identified within 10 min [53].

Jingwu Wang et al. (2008) illustrate daspeedy, selective, and responsive capillary zone electrophoresis (CZE) attached through tris (2,2-bipyridyl) ruthenium(II)-based end-column electrogenerated chemiluminescence (ECL) was utilized to estimate BF in bulk and tablets subsequent to its separation from METO. Tetrahydrofuran were used as an additive in the running buffer to receive the absolute ECL peak of BF. It react with tris (2, 2-bipyridyl) ruthenium (II) ECL system. Under the advanced experimental situation, BF was separated successfully and efficiently from METO and other co-existed materials in tablets and urine samples [54].

Laszlo Gagyiet al. (2008) reported the stereoselective detection of β-blockers by cyclodextrins within capillary zone electrophoresis. This category of medicinal agent was resolved by cardiovascular system disease and its derivativechiral aryloxy-propanolamine. In general, the S (–) enantiomer aremore active than the R (+) enantiomer. Study understand the appliance of a choice of cyclodextrin derivatives, hydroxypropyl-β-cyclodextrins, at randommethylated β-cyclodextrin, sulphated β-cyclodextrin and sulphated α-cyclodextrins for the stereoselective examination of β-blockers. Separation was obtained for BOPI, CARV, MEPI, PIND and ALPR, while only partial separation was observed for SOT, PROP, OXPRE, ATEN, BIS, BUPRA and METO [55].

9. ACCOUNT ON BIO-ANALYTICAL METHOD FOR DETERMINATION OF BF [56-67]

Bioanalytical methods are used for the quantitation of drugs and their metabolites and biological molecule in unnatural location or concentration) and biotic (macromolecule, large molecule drugs and metabolites) in organic systems[56]. Literature survey revealed that LC-MS/MS and HPLC and are predominantly used for the bioanalysis of BF. In Bioanalytical method validation sample is extracted from plasma with help of extraction techniques such as protein precipitation, liquid-liquid extraction and solid phase extraction techniques. In most of methods methanol was used as solvent for extraction of BF in biological fluids. Bioanalytical methods for determination of BF are summarized in [**Table: 5**].

Table 5: Bioanalytical determination of BF.

Sr. No.	Drugs	Biological fluid	Chromatographic conditions	Discussion	Ref
1	BF	Human plasma	RP-C18 column (Inertsil, 4 mm, 150 x 4.6 mm), Methanol: water (70:30, % *v/v*)	*Sevgi Tatar Uluet al.* Described derivatization of BF with 4-chloro-7-nitro-2, 1, 3-benzoxadiazole in borate buffer at pH 9.5 to yield a fluorescent product. Plasma samples (BF and IS) were extracted employing a liquid–liquid extraction method. Ephedrine was used as internal standard. Linearity obeyed in the range of 10 –2,000 ng/mL Retention times was approximately 4.79 min for BF and 3.46 min for IS.	57
2	AMD and BF	Rat plasma	Diamonsil C18 column (50 mm × 4.6 mm, 5 μm), Methanol: water: formic acid (75:25:0.01, % *v/v/v*)	*HuichaoChanget al.* Illustrated a sensitive, specific liquid chromatography–tandem mass spectrometry method for quantitative determination of AMD and BF. The analytes and IS were isolated plasma samples by liquid–liquid extraction. Linearity was followed in the range of 0.2–50 ng/mL and correlation coefficient 0.9961 for both BF and AMD. Retention time 2.12, 1.96 and 1.89 min for both.	58
3	BF	Human plasma	RP-C18 Column (3 × 100 mm, 3.5 μm), 0.1% formic acid solution – acetonitrile (50-50 % *v/v)*	Gabriela Peste *et al.* Developed specific liquid chromatography–tandem mass spectrometrymethoddetermination of BF . The analytes extracted using liquid-liquid extraction method and metoprolol was IS. Linearity obeyed in the range of 1 ng/mL and 100 ng/mL. Correlation Coefficient of 600.99. Retention time, 1.7 min and 1.9 min. result given by BF and METO.	59

Sr. No.	Drugs	Biological fluid	Chromatographic conditions	Discussion	Ref
4	BF	Human plasma	Kromasil C18 column (150 × 4.6 mm,5 µm), Methanol and 0.05% phosphoric acid (40:60 % *v/v*)	Ming Zhang *et al.* developed A three-phase solvent bar microextraction technique combined with high performance liquid chromatography fluorescence detection was for quantitative determination of BF. METO was used as the IS. Linearity obeyed in the range of 10–100 μg/mL Correlation Coefficient was 0.994.	60
5	CEL,BF and IRB	Human plasma	Kromasil C18 column (150 x 4.6 mm,5 µm) phosphate buffer 0.1 M adjusted to pH 3.4 ± 0.1 with hydrochloric acid	*E. Caudron et al.* described method for the simultaneous determination of cardiovascular drugs. Solid-phase extraction technique was used for determination of BF. PROP was used as the IS. Linearity 10–500 ng/ml for CEL is 5–250 ng/ml for BF and 20–1000 ng/mL for IRB. Retention time:-BF: 7.31 CEL: 5.19 IRB: 16.32 Linear Regression Coefficient (r):-CEL 0.9996, BF 0.9990, IRB 0.9994	61
6	BF	Human plasma	Chromolith RP-18e (250 x 4 mm). Kaliumdihydrogen phosphate solution 0.01M, pH 3.5 acetonitrile (77.5:22.5% *v/v/v*)	*CorneliuOniscu et al*. illuminate liquid- liquid extraction with diethyl ether, at alkaline pH, followed by back-extraction with phosphoric acid, and liquid chromatography analysis with fluorescence detection for BF. METO used as IS in this study. Linearity obeys in the range of 3 ng/mL and 200 ng/mL. Retention time was 4.5min and 7.24 min. Correlation coefficient was found 0.99981.	62
7	BF and METO	Human plasma	RP- C18 Nucleosil column acetonitrile–HPLC water with 1.2% (w/v) of triethylamine and the pH adjusted to 3 with 85%orthophosphoric acid (18:82, 20:80, % *v/v*)	*A. J. Brazaet al.* wasdevelopedtwo different liquid–liquid extractions method. Fluorometric detection used for the identification of BF and METOP. Linearity was in the range of 6.25–200 ng/mL for both BF and METO. Retention times for BF and METO were 8.7 and 3.2 min. R 2 = 0.9857 and R 2 = 0.9959.	63
8	CEL and BF	Human skin	C18 Nucleosil column (5-mm 12.5 cm_4 mm), acetonitrile and 67 mM Sorensen's phosphate buffer (pH 5.0) (30/70 % *v/v*)	*P. Modamio et al*. Illustrated a predetermined procedure i.e. RP-HPLC with UV detection which is used for identification of CEL and BF. Phosphate buffer used as a standard solution. Linearity was followed in the range of 25–0.78 µg /mL.	64

Sr. No.	Drugs	Biological fluid	Chromatographic conditions	Discussion	Ref
9	BF	Human plasma	Zorbax SB-C18 (100 mm x 3.0 mm) mixture of methanol and (0.1% (v/v) acetic acid (40:60 % *v/v*) in water at 48 ºC	*Exp Clin Cardiol et al.* was developed multiple reaction monitoring (MRM) mode using an ion trap mass spectrometer equipped with an electro spray ion source for monitoring the BF Methanol was used as an internal standard.LOQ was found for BF 1.78 – 85.44ng/mL. Correlation coefficient greater than 0.993. Retention Time of BF in six different lots of blank plasma (1.9, 2.3, 4.68, 2.3, 3.8, 1.7 min).	65
10	ATEN, BF, HCT, CHLOR, SA, EP and its active metabolite, VAL and FLU.	Human plasma	Luna C18 (150 mm × 4.6 mm, 3 µm), Acetonitrile and watercontaining 0.01% formic acid and 10 mM ammonium formate at pH 4.1	Oskar Gonzalez *et al*. reported simultaneous analysis of several drugs usually combined in cardiovascular therapy. Plasma samples were extracted employing a simple protein precipitation extraction with acetonitrile and pravastatin was used as IS.	66
11	BF	Plasma serum	stainless steel tube (125 x *5* mm ID) 1 mM camphorsulphonic acid in methanol	*R. J. Eastwood et al. reported* measurement of bisoprolol in plasma by using high performance liquid chromatography. Tris solution, benzimidazole which is aqueous internal standard and methyl t-butyl ether mixed with the sample vortex for 30 seconds. After the centrifugation at particular portion resulting extract is analyzed on a micro particulate silica column using 1 mM camphorsulphonic acid in methanol as the mobile phase. At 215 nm detection of limit and detection of quantitation can be calculated. Minimal interference from either commonly prescribed drugs or endogenous compounds can be determined.	67

10. IMPURITY PROFILING ON BF [68-72]

The impurity profiling is designed with objectives to establish specific link between two or more samples, ascending drug distribution pattern, for identification of sources of drug samples and also for monitoring the process for drug manufacturing [68]. According to the ICH guidelines impurities are matter in the product which is not active pharmaceutical ingredients or the excepient used to manufacture it [69].An impurity profile has been established for quantification of BF alone and in combined dosage form. There are a various types of impurities present in BF. Following explanation can be established the impurity present in BF and their combined dosage form.

Table 6: Impurities in Bisoprolol Fumarate.

Sr. No.	Conditions	Number of impurity	Structure of impurities	Ref
1	Evaluation on readymade impurities obtained from vender	2	1. 2.	70

Table 6 : *Contd...*

Sr. No.	Conditions	Number of impurity	Structure of impurities	Ref
2	**1. Forced Degradation Study**:- 1.1 Photo stability study: - light providing an illumination of 1.2million lux-hours (7.1 h) and integrated near-ultraviolet energy of 200Wh/m2 (2.9 h) and then exposed to five times increased irradiance dose. 1.2Oxidative Degradation Study: - Tablets were treated with hydrogen peroxide solution (2% in water, 5 mL). **2. ThermalDegradation Study:** -Mixture directly exposed to 40ºC/75%, for 2, 4, and 8 weeks. 2.1. Thermal Degradation Study A: - Mixture placed onan open quartz Petri dish and kept at 80ºC for 5 hours, for 5 days. 2.2ThermalDegradation Study B: - Mixture was placed in an open quartz Petri dish and kept at 80□C for 72 hours. A temperature of 80□C for 121 hours in an open Petri dish. The result for unidentified impurities was 1.07%.	1	1.	71

Table 6 : *Contd...*

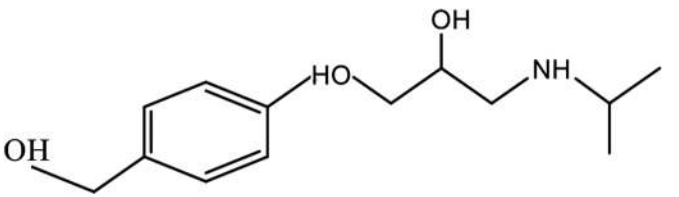
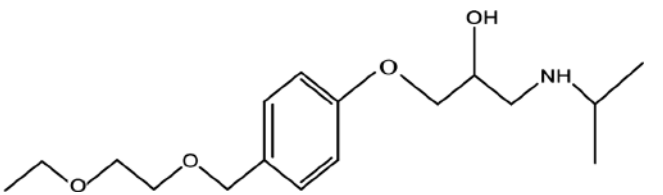
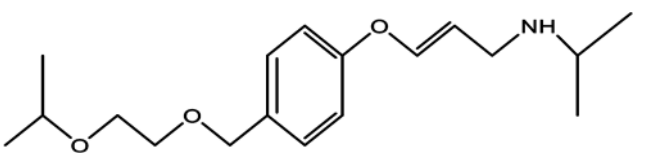
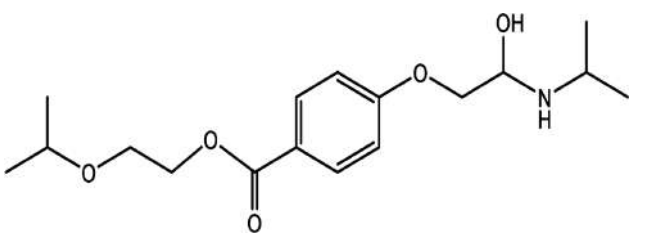
Sr. No.	Conditions	Number of impurity	Structure of impurities	Ref
3	**Force degradation study: -** degradation parameter like acid, base, and peroxide, thermal, photolytic can be used with different conditions like 0.1NHCl at 60°C for 1 hour, 3% of H_2O_2, 60 °C for 72 hour and 0.01N NaOH at 60°C for 30 minutes.	9	**1.**A  2.B  3.E  4. K 	

Table 6 : *Contd...*

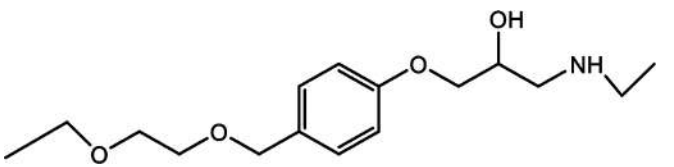
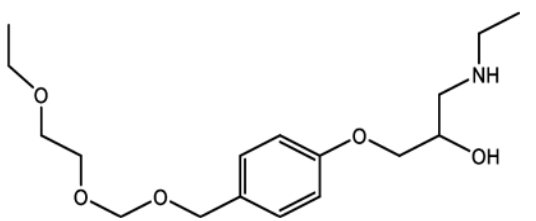
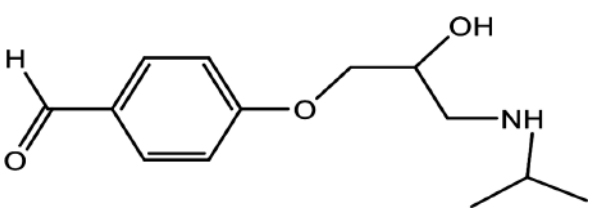
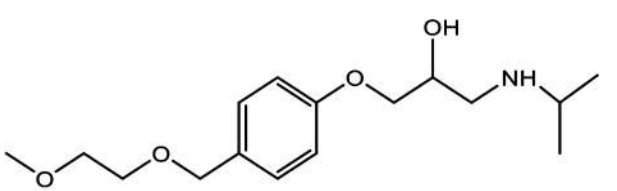
Sr. No.	Conditions	Number of impurity	Structure of impurities	Ref
			5.N 	72
			6.G 	
			7.L 	
			8.Q 	

Table 6 : *Contd...*

Sr. No.	Conditions	Number of impurity	Structure of impurities	Ref
		9.R		
		10.S		

Tijana Rakic et al. (2014) established hydrophilic inter face liquid chromatographic method for study of BF and its impurities A and C. The chemometric strategy was resolved to systems activities and establishing the mathematical association between acetonitrile content which was present in mobile phase, pH of the water phase and buffer concentration in the water phase and chromatographic responses. Investigation all studies of BF from beginning to end Chromatographic technique and its impurities was established on HILIC 100Å (100 mm x 4.5 mm, 2.6 μm particle size); using mobile phase mixture consist was acetonitrile – water phase (35 mM ammonium acetate, pH 4.9 manage with glacial acetic acid) (85:15 *v/v*) with flow rate 1 mL/min and analysis was performed at ambient temperature. Impurities of BF (impurity A and impurity C) are shown in **Table 6** [70].

Ivana Mitrevska et al. (2017) established identification, structural interpretation and qualification of a degradation impurity RRT 0.95 of BF in film-coated tablets. The impurity of relative retention time gives at 0.95 was observed in the stress thermal degradation study of the BF film-coated tablets with identification, characterization and quantitation was performed using HPLC/DAD/ESI-MS method. The configuration of the embattled Impurity RRT 0.95 was shown in **Table 6** with molecular mass of BF were 406 [71].

Venkata Narasimha Rao Ganipisetty et al. (2016) studied twelve impurities of BF and HCT and separated simultaneously using HPLC technique. Out of 12 reported impurities, five were found to be potential degradants. During the validation of stability indicating method, the focus was on the critical parameters in resolving the degradants from the main components. These parameters include Hand, temperature solvents because BF and HCT have different solubilities and polarities. The method was precise (RSD<1.0%), accurate, linear (r2>0.999), robust, and stability indicating in the range of LOQ to 150% [72].

11. ELECTROCHEMICAL METHODS:

11.1 Voltammetric methods for BF: [73-75]

Rajendra N. Goyal et al.(2011) recognized an voltammetric performance of BF by using graphite electrodes were completed with single wall carbon nanotubes. In comparison to BPPGE, EPPGE gives supplementary sharp peaks in oxidation of BF. In the variety 10 – 1000 mV/s in phosphate buffer solution of pH 7.2, the examination rate of repeated voltammogram was assorted. The limits of detection were found to be 2.8×10^{-7} M and 7.3×10^{-7} M [73].*Bozal et al* (2012) wasreported Simultaneous estimation of BF and HCT in their pharmaceutical formulation by applying different voltammetric,

chromatographic, and spectrophotometric analytical methods. The level of difference pulse and square wave voltammetry techniques were used for the analysis of BF and HCT concurrently by measuring at with reference to 1400 and 1100 mv. By using different electrolytes including H_2SO_4, phosphate, acetate, and BR buffers with different pH values between 0.3 and 12.0 containing a constant amount of 20% methanol the voltammetric oxidation of BF and HCT were reported. BF was oxidized between pH 0.3 and 10.

*Rajendra N. Goyal et al. (*2007)studied a BF in pharmaceutical dosage form and urine using single-wall carbon nano tubes customized glassy carbon electrode. The SWNTs-modified GCE exhibited a sharp anodic peak at a potential of 950mV for the oxidation of BF. In good condition linearity was found in the range of 0.01–0.1mM in 0.5M phosphate buffer solution having pH 7.2 with a correlation coefficient of 0.9789 and limit of detection was reported at 8.27×10^{-7} M.

11.2 Potentiometric method for BF: [76-77]

Grzegorzbazylak et al. (2002) reported execution of analytical and biopharmaceutical screening data for beta-adrenergic-drug simple menting many macro cycle in HPLC Systems. In the cation-exchange HPLC technique for the studies applying acetonitrile – 40 mM phosphoric acid (15: 85,% v/v,) as a mobile phase. By employing crossbreed polymer silica packets in RP-HPLC it can be considered that promising surrogate in high throughput drug control process for examination of beta adrenergic agonist in humans and animals recommend the Potentiometric recognition [76].

Saad S.M. Hassan et al. (2003) reported the used of polymeric medium membrane sensors for purpose of β-blockers. This sensor was depending on the cations with tungs to phosphate anion as electro active materials. In some dosage form sensors are implemented for direct potentiometry of β-blockers. for the construction of the sensor plastic membrane can be made by preparing composition 2:34:64% (w/ w) ion pair complex, PVC and DOP plasticizer. The sensor was uncomplicated for the purpose of b-blockers at a concentration level as low as 10^{-7} mol l^{-1} with an accuracy of 99.1 ±/1.3 %. [77].

12. CONCLUSION

The present review gives various analytical methods for the estimation of BF. A different analysis had perform which include, Bio-analytical, HPLC, HPTLC, UV/Vis-Spectroscopy, Spectroflurometry, capillary electrophoresis, stability indicating method, impurity profile and electrochemical method like voltammetric and Potentiometric method for validation of BF in bulk and in

its combined pharmaceutical formulations and in plasma. Through HPLC with UV detection has been found to be most studied for estimation of BF in bulk as well as pharmaceutical dosage forms, while hyphenated LS-MS, Bioanalytical, UPLC methods are reported for quantification of BF and its metabolite in plasma and other biological fluids. HPTLC and Stability-indicating by HPLC and HPTLC are also reported in literature survey. Certain Spectrophometric methods in UV-Visible along with spectroflurometric are most often used for assessment for BF. Various types of stability indicating method and impurity profiling method have been estimated.

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CONFLICT OF INTEREST

Authors do not have conflict of interest for this manuscript.

ABBREVIATIONS

UV	Ultra Violet
VIS	Visible
HPLC	High-Performance Liquid Chromatography
HPTLC	High-Performance Thin-Layer Chromatography),
UPLC	Ultra Pressure Liquid Chromatography,
LC-MS	Liquid Chromatography-Mass Spectrometry
IS	Internal standard
R*f*	Retention factor
Rt	Retention time
BF	Bisoprolol Fumarate
ML	Mili Liter
MP	Melting point
µg	Microgram
IRB	Irbesartan
BIS HEMI F	Bisoprolol Hemifumarate
AMD	Amlodipine
AMD B	Amlodipine Besylate
CELI	Celiprolol

METO T	Metoprolol Tartarate
USP	United State Pharmacopeia
Nm	Nano Meter
TLC	Thin Layer Chromatography
TALINO	Talinolol
MEPIN	Mepindolol
BOPIN	Bopindolol
OXPRE	Oxprenolol
Mm	Mili Meter
CZE	Capillary Zone Electrophoresis
ECL	Electrogenerated Chemiluminescence
BOPIN	Bopindolol
CARV	Carvidilol
MEPI	Mepindolol
PIND	Pindolol
ALPA	Alprenol
SOT	Sotalol
PROP	Propranolol
OXPRE	Oxprenolol
ATEN	Atenolol
BUPRA	Bupranolol
DNA	Dioxyribonucleic Acid
RP-HPLC	Reversed- Phase High-Performance Liquid-Chromatography
SWNT/GCE	Single - Walled Carbon Nanotube /Modified Glassy Carbon Electrode
BUF	Bufralol
CAR	Carazolol
CELEN	Celenbuterol
MABU	Mabuterol
CIM	Cimaterol
ALP	Alprenol
TETR	Tetertolol
BEV	Bevanotolol
TCPB	Tetrakis (P-Chlorophenyl)Borate
CEX –HPLC	Cation-Exchange High Performance Liquid Chromatography
PVC	Polyvinyl Chloride
BOR	borate electrode

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