

TABLE OF CONTENTS

S.No.	Description	Page No.
	Chapter 1: Introduction	1
1.1	Introduction	1
1.2	Classification of Impurities	2
1.3	Sources of impurities	2
1.4	Genotoxic impurity and hazard assessment	2
1.5	Theoretical and Practical Aspects of Liquid Chromatography	4
1.6	Theoretical and practical aspects of mass spectrometry	5
1.6.1	Sources	6
1.6.2	Analyzers	8
1.6.3	Detectors	9
1.6.4	Recording of mass spectra	10
1.6.5	LCMS applications	10
1.7	Method of validation of analytical techniques	11
1.7.1	Specificity and Selectivity	12
1.7.2	Precision	12
1.7.2.1	Repeatability	12
1.7.2.2	Intermediate precision	12
1.7.2.3	Reproducibility	12
1.7.3	Linearity	12
1.7.4	Range	13
1.7.5	Accuracy	13
1.7.6	Solution stability	13
1.7.7	Robustness	13
1.7.8	Limit of detection and limit of quantitation	13
1.8	Aim and objective of the present work	14
	Chapter 2: Literature Survey	17
2.1	Literature survey on atazanavir sulphate and impurities	17
2.2	Literature survey on erlotinib and impurities	18
2.3	Literature survey on imatinib mesylate and its impurities	20

2.4 Literature survey on pantoprazole sodium and its impurities	22
2.5 Literature survey on albendazole and impurities	24
2.6 Literature survey on quantification of genotoxic impurities by GC-MS and LC-MS method	25
Chapter 3: QUANTITATIVE ESTIMATION GENOTOXIC IMPURITY IN ANTIRETROVIRAL DRUG: ATAZANAVIR SULPHATE	27
3.1 Introduction	27
3.2 Experimental	28
3.2.1 Standards and chemicals	28
3.2.2 Preparation of solutions	29
3.2.2.1 Sample preparation	29
3.2.2.2 Preparation of standard BOC epoxide stock solution	29
3.2.2.3 Standard solution preparation	29
3.2.2.4 Preparation of LOD and LOQ solution	29
3.2.2.5 Preparation of accuracy solutions	30
3.2.2.6 Preparation of linearity solutions	30
3.2.2.7 Solution preparation for method precision, intermediate precision and robustness	31
3.2.2.8 Preparation for stability of analytical solution	31
3.2.3 Instrumentation	31
3.3 Results and discussion	32
3.3.1 Method development	32
3.3.2 Operating conditions of LC and MS	32
3.3.3 Validation Study	33
3.3.3.1 Specificity	33
3.3.3.2 Determination of LOD and LOQ	35
3.3.3.3 Recovery Studies	36
3.3.3.4 Linearity	37
3.3.3.5 System suitability	39
3.3.3.6 Precision	39
3.3.3.7 Robustness	40
3.3.3.8 Solution stability	41
3.3.3.9 Application of the method	42

Chapter 4: QUANTIFICATION OF GENOTOXIC IMPURITIES IN ANTI-CANCER DRUGS: ERLOTINIB HYDROCHLORIDE & IMATINIB MESYLATE	43
4.1 ERLOTINIB HYDROCHLORIDE	43
4.1.1 Introduction	43
4.1.2 Experimental	44
4.1.2.1 Standards and chemicals	44
4.1.2.2 Preparation of Solutions	45
4.1.2.2.1 Sample preparation	45
4.1.2.2.2 Preparation of standard stock solution	45
4.1.2.2.3 Preparation of standard Solution	45
4.1.2.2.4 Preparation of LOD and LOQ solution	45
4.1.2.2.5 Solution preparation for accuracy	45
4.1.2.2.6 Solution preparation for linearity	46
4.1.2.2.7 Solution preparation for method precision, intermediate precision and robustness study	47
4.1.2.2.8 Preparation for stability of analytical solution	47
4.1.2.3 Instrumentation	47
4.1.3 Discussion on Results	47
4.1.3.1 Method development	47
4.1.3.2 LC-MS/MS operating conditions	47
4.1.3.3 Validation Study	49
4.1.3.3.1 System Suitability	49
4.1.3.3.2 Specificity	49
4.1.3.3.3 Limit of detection (LOD) and limit of quantification (LOQ)	50
4.1.3.3.4 Linearity	50
4.1.3.3.5 Accuracy	52
4.1.3.3.6 Precision	54
4.1.3.3.7 Robustness	54
4.1.3.3.8 Solution stability	56
4.1.3.3.9 Method application	56

4.2. IMATINIB MESYLATE	57
4.2.1 Introduction	57
4.2.2 Experimental	58
4.2.2.1 Standards and chemicals	58
4.2.2.2 Preparation of Solutions	58
4.2.2.2.1 Sample preparation	58
4.2.2.2.2 Preparation of standard IMT-01 stock solution	59
4.2.2.2.3 Preparation of standard Solution	59
4.2.2.2.4 Preparation of LOD and LOQ solution	59
4.2.2.2.5 Preparation of accuracy solutions	59
4.2.2.2.6 Preparation of linearity solutions	60
4.2.2.2.7 Solution preparation for method precision, intermediate precision and robustness study	61
4.2.2.2.8 Preparation for stability of analytical solution	61
4.2.2.3 Instrumentation	61
4.2.3 Results and discussion	61
4.2.3.1 Method development	61
4.2.3.2 Operating conditions of LC/MS/MS	61
4.2.3.3 Validation Study	62
4.2.3.3.1 Specificity	63
4.2.3.3.2 Determination of LOD and LOQ	64
4.2.3.3.3 Recovery studies	64
4.2.3.3.4 Linearity	66
4.2.3.3.5 System Suitability	67
4.2.3.3.6 Precision	67
4.2.3.3.7 Robustness	68
4.2.3.3.8 Solution stability	70
4.2.3.3.9 Application of the method	71

Chapter 5: DETERMINATION OF GENOTOXIC IMPURITIES IN ANTI ULCER DRUG: PANTOPRAZOLE SODIUM SESQUIHYDRATE	72
5.1 Introduction	72
5.2 Experimental	73
5.2.1 Standards and chemicals	73
5.2.2 Preparation of Solutions	74
5.2.2.1 Preparation of standard stock solution	74
5.2.2.2 Preparation of standard solution	74
5.2.2.3 Preparation of LOD and LOQ solution	75
5.2.2.4 Preparation of accuracy solutions	75
5.2.2.5 Preparation of linearity solutions	75
5.2.2.6 Solution preparation for method precision, intermediate precision and robustness study	76
5.2.2.7 Preparation for stability of analytical solution	76
5.2.2.8 Preparation of sample solution	76
5.2.3 Instrumentation	76
5.3 Results and discussion	76
5.3.1 Method development	76
5.3.2 Operating conditions of LC/MS/MS	77
5.3.3 Validation Study	78
5.3.3.1 Specificity	78
5.3.3.2 Limit of detection (LOD) and limit of quantification (LOQ)	79
5.3.3.3 Linearity	80
5.3.3.4 Accuracy	81
5.3.3.5 System Suitability	84
5.3.3.6 Precision	84
5.3.3.7 Robustness	85
5.3.3.8 Solution stability	87
5.3.3.9 Application of the method	88

Chapter 6: EVALUATION OF GENOTOXIC IMPURITIES IN ANTHELMINTIC DRUG: ALBENDAZOLE	89
6.1 Introduction	89
6.2 Experimental	90
6.2.1 Standards and chemicals	90
6.2.2 Preparation of Solutions	91
6.2.2.1 Sample preparation	91
6.2.2.2 Preparation of standard stock solution	91
6.2.2.3 Preparation of standard solution	91
6.2.2.4 Preparation of LOD and LOQ solution	91
6.2.2.5 Preparation of accuracy solutions	91
6.2.2.6 Solution preparation for linearity	92
6.2.2.7 Solution preparation for method precision, intermediate precision and robustness	93
6.2.2.8 Preparation for stability of analytical solution	93
6.2.3 Instrumentation	93
6.3 Discussion on Results	93
6.3.1 Method development	93
6.3.2 LC-MS/MS operating conditions	93
6.3.3 Validation Study	95
6.3.3.1 System Suitability	95
6.3.3.2 Specificity	95
6.3.3.3 Limit of detection (LOD) and limit of quantification (LOQ)	97
6.3.3.4 Linearity	97
6.3.3.5 Accuracy	98
6.3.3.6 Precision	99
6.3.3.7 Robustness	100
6.3.3.8 Solution stability	102
6.3.3.9 Method application	102
Chapter 7: SUMMARY, CONCLUSION AND RECOMMENDATIONS	103
7.1 Summary	103
7.1.1 Quantitative estimation genotoxic impurity in antiretroviral drug: atazanavir sulphate validation study summary	103

7.1.2 Quantification of genotoxic impurities in Anti-Cancer Drugs: Erlotinib hydrochloride & Imatinib mesylate validation summary	104
7.1.2.1 Erlotinib Hydrochloride validation study summary	104
7.1.2.2 Imatinib mesylate validation study summary	105
7.1.3 Determination of genotoxic impurities in Anti Ulcer Drug: Pantoprazole sodium sesquihydrate validation study summary	106
7.1.4 Evaluation of genotoxic impurities in Anthelmintic Drug: Albendazole validation study summary	107
7.2 Conclusions and recommendation	108
References	109
Index	128
List of Publications	130