REVIEW ARTICLE

VERSATILE APPROACHES FOR ANALYTICAL METHOD VALIDATION OF ANTICANCER DRUGS: A REVIEW

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ABSTRACT

Cancer refers to a group of illnesses that result from cell population in the body increasing unusually. These cells break up and create new cells in an uninhibited mode that can extend in the body and cause injury to vital organs. Analytical chemistry is the division of chemistry involved in separating, identifying and determining the relative quantity of the components in a sample. Analytical method development and validation play vital role in method development and manufacture of pharmaceuticals. The objective of this review article is to study divergent types of anticancer drugs and the different analytical methods assessed during their determination, like UV-Visible Spectrophotometer, GC, Mass Spectrophotometer, NMR, LC-MS, GC-MS and FT-IR. The involvement for analytical methods to establish an anticancer drug is of utmost importance. The development and validation of analytical methods is mandatory for preclinical and clinical studies and even for the development of formulations containing these compounds. This constitutes the next challenge in the analysis of anticancer drugs. This review outlines the recent position of method development and validation of anticancer drugs in bulk and solid dosage forms.

Keywords: Anticancer drug, method development and validation, ICH guidelines, UV Visible spectroscopy, RP-HPLC, LC-MS

INTRODUCTION

Analytical instruments play a major role in method development to get high quality and consistent analytical data. Analytical method development is the process of selecting a precise method to establish the composition of a formulation[1]. Analytical method could be spectral, chromatographic, electrochemical or hyphenated. Method development and validation are continuous and mutually supporting tasks connected with research and development, quality control and quality assurance departments[2,3]. Analytical procedures play a decisive role in equivalence and risk assessment and their management.

Cancer is a disease in which the control of growth is missing in one or more cells, leading to formation of a solid dosage mass of cells known as a tumour or to a blood or bone marrow linked cancer[4]. These cells divide and create new cells in an uninhibited manner that can increase in the body and cause injury to vital organs. Anticancer drugs are grouped according to the therapy as chemotherapy, hormonal therapy, and immunotherapy. Chemotherapeutic drugs include a family defined equally by their chemical structure and mechanism of action: alkylating agents, antibiotics, antimetabolites, topoisomers, primary and secondary inhibitors, mitosis inhibitors and others[5,6].

Alkylating agents: Alkylating agents have been used for the treatment of cancer for more than six decades[7]. These agent acts for the duration of all stages of the cell cycle, directly on DNA, cross linking the N-7- guanine

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residues, cause DNA filament breaks, leading to irregular base combination, disruption of cell distribution and finally resulting in cell death[8,10]. Analytical methods for determination of alkylating agents are summarized in Table I.

Platinum coordination complexes: The platinum coordination complexes are a category of anticancer agents that are typically classified as alkylating agents, but which are of individual types[12]. Their anticancer activity appears to transmit to the fractuous connecting of DNA molecules in a manner analogous to alkylating agent[14]. Analytical methods for determination of platinum coordination complexes are summarised in Table II.

Antimetabolites: Antimetabolites are substances which, by virtue of their comparable chemical structure to vital compounds in the cell, interfere with the consumption of these substances and therefore harmfully affect cell utility and enlargement. Antimetabolites are frequently term "analogues," and different types are well known[16]. Analytical methods for determination of antimetabolites are given in Table III.

Table I: Analytical methods for alkylating agents

Sr. No.	Sub-Class	Drug name	Instrument used for method development	Solvent system	Reference
1.	Nitrogen mustard	Cyclophosphamide	RP-HPLC	A-Water-acetonitrile (9:1V/V) B-Water-acetonitrile (3:7 V/V)	8
			LC-MS/MS	Triple liq.liq. extraction-ethyl acetate-dichloromethane (3:1:6 V/V/V)	9
			SPE-HPLC-MS/MS	Methanol-water (1:1 V/V)	10
			HPLC-UV	0.05M Disodium hydrogen phosphate-acetonitrile (65:35 V/V)	11
			UPLC	Acetonitrile-pH-7.0 buffer (20:80 V/V)	12
			LC	Acetonitrile-water (60:40V/V)	13
			GC-MS	Diethyl ether-ethyl acetate	14
			UV-VIS-Spectrophotometer	0.1N HCl	15
		Ifosphamide	UPLC-MS/MS	Ammonium formate-methanol-acetonitrile (40:48:12 V/V/V)	16
			RP-HPLC	Methanol	17
			SPE-HPLC-UV	Phosphate buffer pH-6.0- acetonitrile (77.25:22.75 V/V/V)	18
		Chlorambucil	UV-Visible-Spectrophotometer	Acetonitrile	19
			LCMS/MS	Methanol	20
		Bendamustine HCl	RP-HPLC	0.1Trifluroacetic acid in water- acetonitrile (90:10 V/V)	21
			RP-HPLC	Trifluroacetic acid and acetonitrile	22

			UV-VIS-Spectrophotometer (Difference spectroscopy)	Phosphate buffer (pH-6.8), Borate buffer (pH-9.0)	23
			UV-Visible Spectrophotometer	Methanol	24
			RP-HPLC	pH 7.0 Buffer: Methanol	25
			UV-Visible Spectrophotometer	Methanol	26
			UV-Spectrophotometer (1st Derivative spectroscopy, Difference spectroscopy)	Phosphate buffer (pH-8.0), boric buffer (pH-9.0)	27
2.	Ethylenimine	Thiotepa	RP-HPLC	Disodium hydrogen phosphate buffer-acetonitrile (85:15V/V)	28
3.	Alkylsulphonate	Busulfan	RP-HPLC	Acetonitrile-water-tetrahydrofuran (66:32:2 V/V/V)	29
			LC-MS assay and HPLC assay	Acetonitrile	30
			RP-HPLC	Methanol-water (80:20V/V)	31
			LC-MS/MS	Acetonitrile-water (1:1 V/V)	32
			LC-MS	Ammonium acetate, formic acid, water, methanol	33
			GC	Ethyl acetate	34
			LC-MS	Acetone	35
			LC-MS	Water, methanol (80:20 V/V)	36
4.	Nitrosoureas	Carmustine	RP-HPLC	Acetonitrile-water (3:7 V/V)	37
		Lomustine	RP-HPLC	Methanol	38
			RP-HPLC	Methanol-acetonitrile	39
			LC	Potasium dihydrogen phosphate-acetonitrile	40
5.	Triazine	Dacarbazine	RP-HPLC	Methanol-phosphate buffer (2:98 V/V)	41
			RP-HPLC	Acetonitrile-0.05 M Disodium hydrogen phosphate	42
			RP-HPLC	Methanol-water (50:50 V/V)	43
		Temozolamide	RP-HPLC	Phosphate buffer-methanol (30:70 V/V)	44
			UV-Spectroscopy	Phosphate buffer	45
			RP-HPLC	Acetic acid-acetonitrile (90:10 V/V)	46

			RP-HPLC	1M HCl	47
			UHPLC-MS/MS	Ammonium formate-acetonitrile	48
			RP-HPLC	Methanol-glacial acetic acid (20:80 V/V)	49
			RP-HPLC	Ammonium acetate buffer-acetonitrile	50
			RP-HPLC	Methanol-glacial acetic acid (20:80 V/V)	51

Table II: Analytical methods for platinum coordination complexes

Sr. No.	Sub-class	Drug name	Instrument used for method development	Solvent system	Reference
1		Cisplatin	RP-HPLC	Water-methanol-acetonitrile (40:35:25 V/V/V)	52
			LC-MS/MS	Methanol	53
			UV-VIS-Spectrophotometer	Phosphate buffer (pH-7.4)	54
			RP-HPLC	Methanol-water (80:20 V/V)	55
			ICP-AES	HCl-Nitric acid (3:1 V/V)	56
			RP-HPLC	Methanol-water-acetonitrile (40:30:30 V/V/V)	57
			MECC	65 mM NaH_2PO_4 - $Na_2B_4O_7$ 4.0mM	58
			UV-VIS-Spectrophotometer	Phosphate buffer saline (pH-7.4)	59
			LC-Electrospray ionization tandem MS	Diethyldithiocarbamate	60
			ICP-MS	Acetonitrile-water	61
			UPLC-ESI-MS/MS	Phosphate buffer-acetonitrile	62
2		Carboplatin	LC/TOF-MS	Methanol-water	63
			UV-VIS-Spectrophotometer (Zero and 1st order derivative)	0.1 N HCl and acetate buffer (pH-4.5)	64
			RP-HPLC	Potassium phosphate (pH-4.5)	65
3		Oxaliplatin	RP-HPLC	Purified water	66
			LC	Acetonitrile and water	67
			RP-HPLC	Methanol-acetonitrile (75:25 V/V)	68
			ICP-MS	HCl-5%,acetic acid-0.1%, thiourea-0.076%, ascorbic acid-0.01%	69
			RP-HPLC	Phosphoric acid-methanol	70

Table III: Analytical methods for antimetabolites

Sr. No.	Sub-class	Drug name	Instrument used for method development	Solvent system	Reference
1.	Folate antagonists	Methotrexate	UV-Visible-Spectrophotometer	HCl-acetonitrile	71
			RP-HPLC	pH-6.0 buffer : acetonitrile (93:7 %V/V)	72
			RP-HPLC	Water-acetonitrile-tetrahydrofuran (65:30:5 V/V/V)	73
			RP-HPLC	0.01 M Phosphate buffer-acetonitrile (89:11 %V/V)	74
			RP-HPLC	Methanol-orthophosphoric acid (70:30 V/V)	75
			UV-VIS-Spectrophotometer and HPLC	Phosphate buffer (pH-6.4)	76
			RP-HPLC	Acetonitrile-potassium dihydrogen orthophosphate (92:8 V/V)	77
			RP-HPLC	0.05 M Sodium phosphate buffer-tetrahydrofuran (95:5 V/V)	78
			RP-HPLC	Distilled water-acetonitrile with formic acid (80:20 V/V)	79
		Pemetrexed	HPLC and UV-Spectrophotometer	20mM Dibasic phosphate buffer-acetonitrile (88:12 V/V)	80
			RP-HPLC	Acetonitrile-sodium dihydrogen orthophosphate (35:65 V/V)	81
			RP-HPLC	1.0 mL Orthophosphoric acid : acetonitrile (85:15 V/V)	82
			RP-HPLC	Acetonitrile	83
			RP-HPLC	Acetonitrile-orthophosphoric acid (15:85 V/V)	84
			LC-MS	Formic acid-acetonitrile	85
2.	Purine antagonists	Azathioprine	RP-HPLC	Acetonitrile-water (50:50 V/V)	86
			RP-HPLC	Acetonitrile-water-methanol (25:70:05 V/V/V)	87
			RP-HPLC	Acetate buffer-acetonitrile-methanol (30:35:35 V/V/V)	88
			RP-HPLC	Potassium dihydrogen phosphate-acetonitrile (60:40 V/V)	89
			UV-VIS-Spectrophotometer	Methanol	90
		Fludarabine	RP-HPLC	Acetonitrile-water (10:90 V/V)	91

			RP-HPLC	Potassium dihydrogen phosphate (pH-6.0)-methanol (96:4 V/V)	92
			RP-HPLC	pH-4 Orthophosphoric acid-methanol (95:5 V/V)	93
			RP-HPLC	Perchloric acid	94
			UV-VIS-Spectrophotometer	Distilled water	95
			RP-HPLC	Methanol-water (50:50 V/V)	96
3.	Pyrimidine antagonists	Capecitabine	RP-HPLC	Phosphate buffer-acetonitrile (80:20 V/V)	97
			RP-HPLC	Methanol-ammonium acetate buffer pH-4.5 (60:40 V/V)	98
			RP-HPLC	0.01M Potassium dihydrogen phosphate-methanol (40:60 V/V)	99
			RP-HPLC	Methanol-acetonitrile-water (80:20:80 V/V/V)	100
			RP-HPLC	Methanol-buffer (70:30 V/V)	101
			RP-HPLC	Acetic acid-methanol-acetonitrile (35:60:5 V/V/V)	102
			RP-HPLC & UV-Spectrophotometer	0.1% Acetic acid-acetonitrile (35:65 V/V)	103
			UV-VIS-Spectrophotometer	Methanol	104
			UPLC & HPLC	Acetic acid-water-acetonitrile (11:2:7 V/V/V)	105
			UV-VIS-Spectrophotometer	Distilled water	106
			HPTLC	Toluene-methanol (7.5:2.5 V/V)	107
		Cytrabine	RP-HPLC	Acetonitrile-ammonium acetate(buffer) (30:70 V/V)	108
			RP-HPLC	Acetonitrile-purified water (2:98 V/V)	109
			HPLC-MS/MS	Acetonitrile-methanol	110

Table IV: Analytical methods for microtubule damaging agents

Sr. No.	Sub-class	Drug name	Instrument used for method development	Solvent system	Reference
1.	Vinca alkaloids	Vincristine	HPLC-UV-Spectrophotometer	Acetonitrile 90% in water-phosphate hydrogen phosphate buffer (32:68 V/V)	111
			UV-VIS-Spectrophotometer	Purified water	112
			RP-HPLC	Methanol	113
			RP-HPLC	0.02M Sodium dihydrogen phosphate-methanol (36:64 V/V)	114

			HPTLC	Toluene-methanol-diethylamine (8.75:0.75:0.5 V/V/V)	115
			RP-HPLC	Water-diethylamine-acetonitrile-methanol (34.9:0.1:40:25 V/V/V/V)	116
			UPLC-MS-MS	Methanol	117
		Vinblastine	RP-HPLC	Methanol-acetonitrile-ammonium acetate buffer with 0.1% triethylamine (15:45:40 V/V/V)	118
			RP-HPLC	Methanol-phosphate buffer-acetonitrile	119
		Vinorelbine	RP-HPLC	Phosphate buffer-methanol (40:60 V/V)	120
			HPLC-UV	Acetate buffer-methanol (85:15)	121
			RP-HPLC	Acetonitrile-water (60:40 V/V)	122
			RP-HPLC	Diethyl ether	123
2.	Taxanes	Paclitaxel	RP-HPLC	Acetonitrile-water (70:30, 0.1% trifluoro acetic acid)	124
			RP-HPLC	Methanol-water (80:20 V/V)	125
			RP-HPLC	Acetonitrile-water	126
			RP-HPLC	Methanol-acetonitrile-water (40:40:20 V/V/V)	127
			RP-HPLC	Phosphate buffer saline pH-7.4 with dichloromethane	128
			RP-UFLC	Acetonitrile-phosphate buffer (50:50 V/V)	129
			RP-HPLC	Acetonitrile-water (50:50 V/V)	130
			RP-HPLC	Acetonitrile-phosphate buffer (80:20 V/V)	131
			RP-HPLC	Acetonitrile-water (70:30 V/V)	132
			RP-HPLC	Acetonitrile: water (60:40 V/V)	133
			RP-HPLC	Acetonitrile-phosphate buffer (60:40 V/V)	134
3.		Docetaxel	RP-HPLC	Acetonitrile-triple distilled water (40:60 V/V)	135
			RP-HPLC	0.2% Triethylamine-acetonitrile (45:55 V/V)	136
			RP-HPLC	0.1% Ammonium acetate-acetonitrile (55:45 V/V)	137
			RP-HPLC	Acetonitrile-water (60:40 V/V)	138
			RP-HPLC	Water and acetonitrile	139
			RP-HPLC	Phosphate buffer (pH-3.6)- acetonitrile (27:73 V/V)	140
			UPLC	Acetonitrile-water (60:40V/V)	141
			ESI-MS/MS	0.1% Formic acid in methanol	142
			UV Spectrophotometer	Acetonitrile	143

Table V: Analytical methods for topoisomerase-2 inhibitors

S. No.	Sub-class	Drug Name	Instrument used for method development	Solvent system	Reference
1.		Etoposide	RP-HPLC	Acetonitrile-water (45:55 V/V)	144
			RP-HPLC	Methanol-phosphate buffer (pH-6) (80:20 V/V)	145
			RP-HPLC	Acetonitrile-acetic acid (70:30 V/V)	146
			RP-HPLC	Methanol-water	147
			RP-HPLC	Water-methanol-acetonitrile (40:35:25 V/V/V, pH 3.5)	148
			LC	Acetonitrile-water (35:65 V/V)	149
			HPLC-UV	Water-acetonitrile (70:30 V/V)	150
			RP-HPLC	Sodium acetate buffer pH-4.0-acetonitrile (70:30 V/V)	151
			HPTLC	Dichloromethane-methanol-formic acid (9.5:0.5:0.5 V/V/V)	152
		Topotecan	RP-UPLC	0.1 V/V Orthophosphoric acid in water-acetonitrile	153
			HPLC-MS	0.1% Acetic acid in acetonitrile and 0.5% acetic acid in water	154
			LC-MS/MS	0.1% Formic acid and methanol	155
			RP-HPLC & LC-MS	Methanol-isopropyl alcohol (750:250 V/V)	156
		Irinotecan	RP-HPLC	Acetic acid-acetonitrile-methanol (60:20:20 V/V/V)	157
			LC	Acetonitrile-sodium dihydrogen phosphate dehydrate buffer	158
			RP-HPLC	Acetonitrile- phosphate buffer (60:40 V/V)	159
			RP-HPLC	Phosphate buffer –acetonitrile (75:25 V/V)	160
			HPLC-MS	0.1% Acetic acid/bidistilled water and 0.1% acetic acid/ Acetonitrile	161
			RP-HPLC	Methanol-water (60:40 V/V)	162
			RP-HPLC	Acetonitrile-phosphate buffer (80:20 V/V)	163
			RP-HPLC	Water-acetonitrile (57:43 V/V)	164
			UV-VIS-Spectrophotometric	Toluene-ethyl acetate-methanol-carbon tetrachloride (9.2:5:0.9:0.8 V/V/V/V)	165

Table VI: Analytical methods for antibiotics

Sr. No.	Sub-class	Drug Name	Instrument used for Method development	Solvent system	Reference
1		Doxorubicine	RP-HPLC	Acetonitrile-ammonium hydrogen phosphate (45:55 V/V)	166
			RP-HPLC	0.05mM Ammonium acetate-methanol-acetonitrile (50:25:25 V/V/V)	167

			RP-HPLC	Acetonitrile-0.01M o-phosphoric acid (40:60 V/V)	168
			RP-HPLC	Acetonitrile-buffer (pH-3.0) (40:60 V/V)	169
			RP-HPLC	0.1%OPA-Acetonitrile (45:55 V/V)	168
			RP-HPLC	Acetonitrile-water (30:70 V/V)	169
			HPLC-MS/MS	0.05 M Ammonium acetate-acetonitrile (40:60 V/V)	170
2		Daunorubicin	RP-HPLC	Acetonitrile-methanol-sodium lauryl sulphate (9:1:10 V/V/V)	171
			RP-HPLC	Methanol-acetonitrile (75:25 V/V)	172
			RP-HPLC	0.1% OPA-acetonitrile (55:45 V/V)	173
			RP-HPLC	Methanol-phosphate buffer (60:40 V/V)	174
3		Epirubicin	RP-LC	Acetonitrile-water (30:70 V/V)	175
			RP-HPLC	Acetonitrile-methanol (80:20 V/V)	176
			RP-HPLC	Phosphate buffer-acetonitrile (50:50 V/V)	177
4		Mitomycin C	HPLC-MS/MS	Acetonitrile-isopropanol-water (20:45:35 V/V/V)	178

Table VII: Analytical methods for miscellaneous anti-cancer drugs

Sr. No.	Sub-Class	Drug Name	Instrument used for method development	Solvent system	Reference
1		Hydroxyurea	LC	Sodium acetate-acetonitrile	179
			LC	Acetonitrile-water (6.7:7.7 V/V)	180
			HPLC-UV	Ammonium acetate-acetonitrile	181
			RP-HPLC	0.2 M Sodium perchlorate-methanol (95:5 V/V)	182
2		L-asparaginase	UPLC-MS/MS	Ammonium formate- formic acid in Acetonitrile	183
3		Tretinoin	RP-HPLC	Acetonitrile-methanol (90:10 V/V)	184
			RP-HPLC	Water-glacial acetic acid (90:2 V/V)	185
			RP-HPLC	Trifluoroacetic acid-acetonitrile (15:85 V/V)	186

Microtubule damaging agents: The microtubule damaging agents are an effective category of cancer drugs with equal therapeutic benefit both in hematopoietic and solid tumours. A large number of natural agents and their analogues connect to soluble tubulin and directly to tubulin in the microtubules[111]. Most of these compounds are antimitotic agents which are able to inhibit cell growth increase by acting on the polymerization dynamics of spindles, which are necessary to proper spindle purpose of microtubules. The particular effects of MDAs on the polymer accumulation and the active constancy of the microtubules are complex[114]. Analytical methods for determination of microtubule damaging agents are discussed in Table IV.

Topoisomerase-2 inhibitors: Topoisomerase-2 inhibitors are chemical compounds used to block the act of topoisomerase (topoisomerase-2), which is a type of enzyme that controls the changes in DNA formation by catalyzing the splitting and rejoining of the phosphodiester spine of DNA strands throughout the regular cell cycle.Topoisomerases contain sites which are well-defined targets for cancer chemotherapy treatment. It is considered that topoisomerase inhibitors block the ligation action of the cell cycle, generating specific and dual-trapped breaks that damage the reliability of the genome. Introduction of these breaks then leads to apoptosis and cell death.Analytical methods for determination of topoisomerase-2 inhibitors are summarised in Table V.

Topoisomerase-1 inhibitors:Topoisomerases are DNA enzymes that manage the topology of the supercoiled DNA doubleloop throughout the transcription

of reproduction of cellular genetic materials[144]. Topoisomerase 1 inhibitors are a new group of anticancer agents with a mechanism of action intended to interrupting DNA imitation in cancer cells, the effect of which is cell death. Most, if not all Topoisomerase 1 inhibitors, are derivatives of the plant extract camptothecin. Irinotecan (CPT-11), a semi-synthetic derivative of camptothecin, is accepted in the United States for the treatment of colorectal cancer[146].

Antibiotics: Anticancer or antitumor antibiotics act in a manner comparable to quinolones. The major distinction among antibiotics and antineoplastic antibiotics is that the former act on bacterial cells, while the latter act on cancerous cells in the human body[156]. Antineoplastic antibiotics affect DNA combination and reproduction by inserting into DNA strands or by producing superoxide that cause breaking of DNA strands and prevent the tumorous or cancerous cells to break up further[166]. Analytical methods for determination of antibiotics are given in Table VI.

Miscellaneous: Miscellaneous agents are different from the major classes of cytotoxic agents. General miscellaneous agents are asparaginase and hydroxyurea. These anticancer drugs act on increased cell divisions i.e. are antiproliferative. Due to their dissimilar mechanisms, development and growth of neoplastic cells is inhibited[176]. They also affect rapidly separating normal cells, therefore are able to repress the bone marrow, repress enlargement, damage healing, cause infertility and hair loss[178, 181]. Analytical methods are summarized in Table VII.

CONCLUSION

Worldwide, cancer is a dangerous disease which is very significantly affecting the human population. Research and development for anticancer drugs have been the largest activity in the pharmaceutical industry in terms of the number of projects, clinical trials and spending. The different types of anticancer drugs are analyzed by using a variety of analytical methods like HPLC, GC, GC-MS, NMR, UPLC, LC-MS, Mass-Spectrophotometry, UPLC-MS/MS, LC, ESI-MS/MS, UV-VIS-Spectrophotometer and LC-UV. Analytical methodology provides analysts, researchers, industries and academicians the essential data for a specified analytical problem, sensitivity, accuracy, range of analysis and form the minimum requirement which basically is the specification of the technique. The methods which are mentioned in this review and additional methods that can be developed on this basis can be applied to diverse areas like drug testing and routine analysis in bio-analysis and quality control in pharmaceutical industries.

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