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LIQUID CHROMATOGRAPHICAL METHODS FOR DETERMINATION OF SELECTED ANTICANCER DRUGS: A REVIEW

Reehana.SK* and Suneetha A.

Department of Pharmaceutical Analysis, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, 522001 Andhra Pradesh, India.

***Corresponding Author: Dr. Reehana.SK**
Department of Pharmaceutical Analysis, KVSR Siddhartha College of Pharmaceutical Sciences, Vijayawada, 522001 Andhra Pradesh, India.

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ABSTRACT
This review summarises the analytical techniques presented in the literature for the separation as well as quantification of anticancer drugs in biological matrices and pharmaceutical formulations using several liquid chromatographic methods, like HPLC and LC-MS/MS.

KEYWORDS: Cancer, Analytical procedures, Mass spectrometry, Liquid chromatography.

INTRODUCTION

Tyrosine kinases are enzymes that phosphorylate proteins to activate them. Tyrosine Kinase Inhibitors[1-9] is a type of anticancer medication that works by competing with adenosine triphosphate to prevent phosphorylation (ATP). The variety of chemical structures seen in a select group of anticancer medications encourages researchers to look into the availability of quick, sensitive, selective, and precise analytical approaches on the basis of Mass spectrometry and Liquid chromatography[10-36] for the quantitative detection of these compounds.

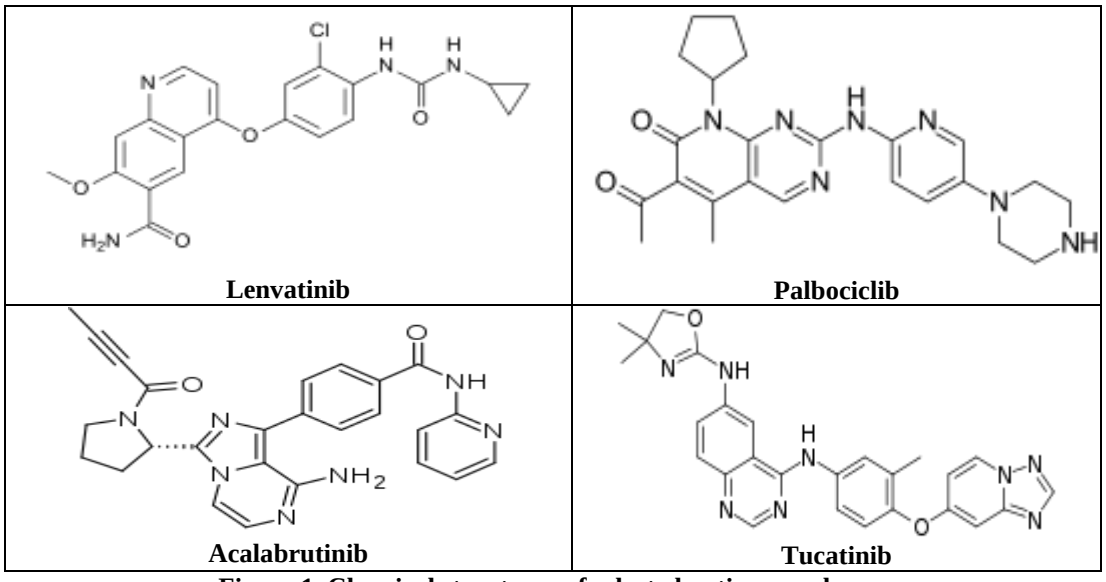

Figure 1. Chemical structures of selected anticancer drugs.

4-["3-chloro-4-(cyclopropyl carbamoylamino) phenoxy"]-7-methoxyquinoline-6-carboxamide is a Lenvatinib chemical name. The drug was authorized in the year 2015 for differentiated thyroid cancer treatment.[37-44] Palbociclib is a chemically known, "6-acetyl-8-cyclopentyl-5-methyl-2-[(5-piperazin-1-ylpyridin-2-yl) amino] pyrido [2, 3-d] pyrimidin-7-one" was authorized in the year 2015 for HER2-negative as well as HR-positive breast cancer treatment.[45-51] The Acalabrutinib's chemical name is,4-["8-amino-3-[(2S)-1-but-2-ynoylpyrrolidin-2-yl"] imidazon[1,5-a] pyrazin-1-yl]-N-pyridin-2-yl benzamide acts as a new irreversible 2nd generation kinase inhibitor of Bruton's tyrosine was authorized in the year 2017 for mantle cell lymphoma

treatment.[52-61] Tucatinib is a chemical "6-N-(4, 4-dimethyl-5H-1, 3-oxazol-2-yl)-4-N-[3-methyl-4-([1,2,4] triazolo[1,5-a] pyridine7-yl oxy)phenyl]" quinazoline-4, 6-diamine was authorized in the year 2020 for metastatic HER2-positive breast cancer treatment.[62-70]

1. Liquid chromatography Mass spectroscopy methods

1.1. Lenvatinib

Using stable isotopically labelled molecules of every kinase inhibitor as internal standards, Aghai et al[71] designed the LC-MS-MS ("Liquid Chromatography-Tandem Mass Spectrometry") approach for simultaneous detection of lenvatinib and nine other kinase inhibitors in bodily fluids. Janssen et al.[72] designed and validated the LC-MS-MS approach for determining lenvatinib, palbociclib, and seven other anticancer medicines. Using propranolol as an internal reference, Tomoko Ogawa-Morita et al.[73] founded the LC-MS-MS approach to measuring Lenvatinib in human plasma. Srikanth et al[74] used Lenvatinib-D4 as an internal standard to create a LC-MS-MS technique for lenvatinib EXfor human plasma. For the quantification of total and unbound lenvatinib, Mano et al[75] established the LC-MS-MS approach and equilibrium dialysis. E7080 (lenvatinib) and its metabolites were determined in feces, human plasma, and urine, as well as whole blood, with LC-MS/MS procedures established by Dubbelman et al.[76]

1.2. Palbociclib

For therapeutic drug monitoring investigations, Llopis et al[77] described a LC-MS-MS approach for measuring palbociclib, as well as eight additional kinase inhibitors, two Anti-androgen drugs, and two active metabolites. Jolibois et al[78] developed an approach to evaluating the concentrations of palbociclib, six anticancer medicines, and its main active metabolite. Posocco et al.[79] established LC-MS-MS for clinical usage for the simultaneous estimate of palbociclib, letrozole, and ribociclib. Al-Shehri et al.[80] developed the Ultra High-Pressure LC-MS/MS approach for the simultaneous measurement of letrozole, palbociclib, and their metabolite in rats' plasma. LC-MS-MS approach was developed by Leenhardt et al[81] for the measurement of palbociclib and ribociclib in plasma. For the evaluation of ribociclib, palbociclib, and abemaciclib in mouse and human plasma, tissue homogenates, Martnez-Chávez et al[82] developed LC-MS-MS. Paul et al[83] investigated the pharmacokinetic interactions of green tea extracts with palbociclib in Sprague Dawley rats by LC-MS-MS. Chavan et al[84] investigated palbociclib metabolism in Sprague–Dawley rats using UPLC–quadrupole time-of-flight tandem MC. Smith et al[85] proposed that the Hamilton PPT approach be used for routine analysis of palbociclib plasma samples taken from micro-sampling PK/PD and PK samples. To assess palbociclib in mouse tumor tissues and human breast tumor xenografts using SCID-beige mice, Nguyen et al[86] developed & validated a sensitive LC-MS/MS approach.

1.3. Acalabrutinib

In beagle dog plasma, Jiang et al[87] developed UPLC-MS/MS for the study of ibrutinib, acalabrutinib, as well as their metabolites. For the measurement of acalabrutinib in Sprague Dawley rats, Surendran et al[88] developed LC-MS-MS.

The conditions for the above-mentioned methods are shown in Table. 1.

Table 1: Liquid chromatography Mass spectroscopy approaches for determination of Anti-Cancer drugs (ACD)

Ref	ACD	Matrix	Column	Mobile phase	Elution	Detection
[71]	***Lenvatinib*** (trametinib, ruxolitinib, osimertinib, nilotinib, dabrafenib, cabozantinib, bosutinib, axitinib, afatinib)	Human serum & plasma	Waters XBridge® Phenyl (2.1× 50) 3.5µ	Phase A: Water-methanol (9:1) and Phase B: Methanol water (9:1) with 10mM Ammonium Bicarbonate	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[72]	***Lenvatinib***, ***Palbociclib***, (ribociclib, osimertinib**,** nintedanib, cobimetinib, alectinib, vismodegib vorinostat)	Human plasma	Gemini C18column (50 × 2.0) 5µ		Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[73]	***Lenvatinib***	Human plasma	XTerra MS C18	0.1percent formic acid in water: acetonitrile	Gradient	Quadrapole mass spectrometer in electrospray ionization

						positive mode
[74]	***Lenvatinib***	Human plasma	Zorbax Eclipse XDB-C18 (4.6x150) 5µ	0.1percent formic acid in water: acetonitrile (20:80)	Isocratic	a quadrupole mass spectrometer operating in turbo ion spray ionization positive mode
[75]	***Lenvatinib***	Human serum	Symmetry Shield TMRP8	Acetonitrile: Ammonium acetate (pH 4.0) (3:2)	Isocratic	Quadrapole mass spectrometer in electrospray ionization positive mode
[76]	***Lenvatinib***	Biological matrices	XTerra MS C18 (2.1× 50) Symmetry Shield RP8 (150 ×2.1)	Acetonitrile: 0.1percent formic acid in water	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[77]	***Palbociclib***, enzalutamide abiraterone sorafenib N-oxide imatinib N-desmethyl Vemurafenib sorafenib ruxolitinib nilotinib imatinib ibrutinib dasatinib cobimetinib	Human plasma	Waters Acquity UPLC®T3 HSS C18	-	Gradient	positive ionization mode of a triple-quadrupole tandem mass spectrometer
[78]	***Palbociclib*** cabozantinib pazopanib sorafenib sunitinib N-desethyl-sunitinib olaparib	Blood plasma	Zorbax Bonus-RP (150x2.1, 1.8µ)	Acetonitrile: water in 0.1% formic acid (92:8)	Isocratic	Quadrapole mass spectrometer in electrospray ionization positive mode
[79]	***Palbociclib*** ribociclib letrozole		Luna Omega Polar C18 column (3µ, 50x2.1)	Water in phase A with 0.1percent HCOOH & Methanol and isopropanol (9:1) in phase B with 0.1percent HCOOH	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[80]	***Palbociclib*** letrozole carbinol	Rat plasma	Acquity_ UPLC BEH C18 (1.7lµ, 50x2.1)	Methanol: water comprising 0.1percent acetic acid (55:45) pH 4.5	Isocratic	Quadrapole mass spectrometer in electrospray ionization positive mode
[81]	***Palbociclib*** ribociclib	Blood plasma	Waters Symmetry® C18 column (4.6 x 75, 3.5µ).	0.1percent Formic acid in water (phase A) as well as in Acetonitrile (phase B)	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[82]	***Palbociclib*** abemaciclib, ribociclib	Human and mouse plasma	Gemini C18 (50 × 2.0, 5µ)	Phase A uses 10 mM ammonium bicarbonate in water and Phase B uses 10mM ammonium bicarbonate in water & methanol (1:9)	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[83]	***Palbociclib***,	Sprague Dawley rats	Waters Acquity BEH C18 (100x 2.1, 1.7µ)	Acetonitrile: 0.1% formic acid	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode

[84]	***Palbociclib***,	Sprague Dawley rats	Waters Acquity BEH C18 (100x 2.1, 1.7µ)	Acetonitrile: 0.1% formic acid	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[85]	***Palbociclib***,	Human plasma	Agilent microbore C18 (1.0 × 50, 3.5µ)	0.1percent formic acid in water (phase A) and acetonitrile (phase B)	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[86]	***Palbociclib***,	SCID-beige mice.	Polaris C8-A (50 × 2.0, 5µ)		Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[87]	***Acalabrutinib***brutinib, ("ACP-5862 PCI-45227")	Beagle dog plasma.	Acquity BEH C18 (2.1×50, 1.7µ)	Acetonitrile: 0.1% formic acid	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode
[88]	***Acalabrutinib***	Rat plasma	Agilent Eclipse Plus C8 column (50×4.6)	10mM ammonium formate: acetonitrile	Gradient	Quadrapole mass spectrometer in electrospray ionization positive mode

2. Liquid chromatography methods

2.1. Lenvatinib

Temgire[89] and co-workers develop an accurate HPLC approach for determining the concentration of the anticancer medication Lenvatinib in capsules. Sultana[90] and coworkers developed a new UPLC method for determining Dasatinib and Lenvatinib in pharmaceuticals. Veni et al[91] established a method for determining lenvatinib and the internal standard methotrexate in human plasma using liquid chromatography. Laxmikanth[92] and colleagues developed an HPLC method for determining lenvatinib in medicines. The HPLC method for determining lenvatinib mesylate in pharmaceuticals was developed by Bandla et al.[93] For the detection of Lenvatinib in pharmaceuticals, Prashanthi et al[94] developed a reverse-phase chromatographic technique. The RP HPLC method for determining Lenvatinib Mesylate in pharmaceuticals was developed by Uttam Prasad et al.[95]

2.2. Palbociclib

Panda et al[96] used chemometrics to develop a reverse-phase chromatographic technique for determining palbociclib in pharmaceuticals. The HPLC method for determining palbociclib in the biological fluid was developed by Nalanda et al.[97] To estimate Palbociclib and Letrozole, Dange, et al[98] presented a reverse-phase chromatographic technique. The RP HPLC method for palbociclib measurement was developed by Kallepalli et al.[99]

1.3. Acalabrutinib

For the detection of Acalabrutinib in capsules, Anusha et al[100] developed a reverse-phase chromatographic technique. The HPLC method for quantifying Acalabrutinib was developed by Priyanka et al.[101]

The conditions for the above-mentioned methods are shown in Table. 2.

Table 2: LC approaches for the determination of Anti-Cancer drugs.

Ref	ACD	Matrix	Column	Mobile phase	Elution	Detection
[89]	***Lenvatinib***	Pharmaceuticals	Inert Sustain C18 (250 ×4.6) 5µ	"Water: Acetonitrile: Trifluoroacetic acid (60:40:0.1)"	Isocratic	UV=241 nm
[90]	***Lenvatinib*** and Dasatinib	Pharmaceuticals	Waters Acquity C8	"Sodium phosphate buffer (pH 3.5): Methanol (60:40)"	Isocratic	UV=276 nm
[91]	***Lenvatinib***	Human plasma	Zodiasil C18 (150 × 4.6) 5µ	Sodium dihydrogen phosphate (pH4.8): Acetonitrile (45:55)	Isocratic	UV=240 nm
[92]	***Lenvatinib***	Pharmaceuticals	ODC (250 x 4.6), 5µ	Ammonium acetate:Acetonitrile (90:10)	Isocratic	UV=367 nm
[93]	***Lenvatinib***	Pharmaceuticals	UPLC HSS C18 (100× 2.1) 1.8µ	0.1percent Ortho phosphoric acid: Acetonitrile (50:50)	Isocratic	UV=240 nm
[94]	***Lenvatinib***	Pharmaceuticals	YMC C18	Water: Methanol	Isocratic	UV=240 nm

			(150 × 4.6) 5µ	(30:70)		
[95]	***Lenvatinib***	Pharmaceuticals	Kromasil C18 (250 × 4.6) 5µ	Ammonium acetate (pH 3.5): Acetonitrile (30:70)	Isocratic	UV=309 nm
[96]	***Palbociclib***	Pharmaceuticals	Reverse phase	Methanol: Potassium dihydrogen phosphate buffer (70:30) (pH 3.5)	Isocratic	UV=265 nm
[97]	***Palbociclib***	Human plasma	Agilent Zorbax C18 (150 × 4.6) 5µ	Acetonitrile: 0.1% Triethylamine (pH 3.3) (70:30)	Isocratic	UV=266 nm
[98]	***Palbociclib*** and Letrozole	Pharmaceuticals	Inertsil C8 (250 × 4.6) 5µ	"Sodium dihydrogen phosphate buffer (pH 5.5): Acetonitrile: Methanol (80: 10:10)"	Isocratic	UV=254 nm
[99]	***Palbociclib***	Pharmaceuticals	Inertsil ODS-3V(250 × 4.6) 5µ	Ammonium acetate: Acetonitrile (32:68)	Isocratic	UV=263 nm
[100]	***Acalabrutinib***	Pharmaceuticals	Zodiasil C18 (150 × 4.6) 5µ	Water: Methanol (60:40)	Isocratic	UV=236 nm
[101]	***Acalabrutinib***	Pharmaceuticals	Kromasil C18 (250 × 4.6) 5µ	0.1% Orthophosphoric acid: Methanol (50:50)	Isocratic	UV=236 nm

CONCLUSION

This critical review of the analytical approaches for identifying selected anticancer drugs in biological matrices and pharmaceuticals that have been published in the literature is useful for pharmacokinetic studies and quality-control tests, as well as therapeutic drug monitoring studies in routine clinical practice.

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