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QUALITATIVE AND QUANTITATIVE ESTIMATION OF TYROSINE KINASE INHIBITORS IN PHARMACEUTICAL AND BIOLOGICAL MATRICES - AN OVERVIEW

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ABSTRACT: Tyrosine kinase inhibitors generally having a narrow therapeutic window and large inter-patient variability. In order to support its therapeutic drug monitoring, fast and accurate methods are needed to supporting the pharmacokinetic-guided dosing in patients treating with various tyrosine kinase inhibitors (TKIs) either alone or in combination in bulk, formulations or human plasma using HPLC and detection with tandem mass spectrometry (HPLC-MS/MS), gas chromatography with mass spectrometry, spectrofluorimetry and UV-Visible spectrometry. Literature suggested that the methods developed and validated are good for accuracy, precision, and assay for all TKIs studied. These methods are also applied for routine therapeutic drug monitoring and investigator-initiated research. In this review, we described different analytical methods used for the qualitative and quantitative estimation of all TKIs investigated till 2020 in assessing the quality of drugs by using HPLC, LC-MS, HPTLC, UPLC, UV-Visible spectrophotometry, spectrofluorimetry with a huge survey from the research articles published in various pharmaceutical and analytical chemistry journals. From this assessment, these methods were found to be superior based on the quantitative analysis of drugs in API, formulations, biological fluids such as serum and plasma. Detailed validation parameters are also given for the methods that help the researchers select suitable analytical techniques based on the information sought.

INTRODUCTION: There are different types of growth factors [Epidermal Growth Factor (EGF), Vascular Endothelial Growth Factor (VEGF), Platelet-Derived Endothelial Growth Factor (PDGF), and Fibroblast Growth Factor (FGF)] which are produced by the body in order to control the cell growth **Fig. 1.** There are different types of growth factor blockers [*e.g.*, Tyrosine Kinase - Inhibitors (TKIs), Proteasome Inhibitors (PIs),

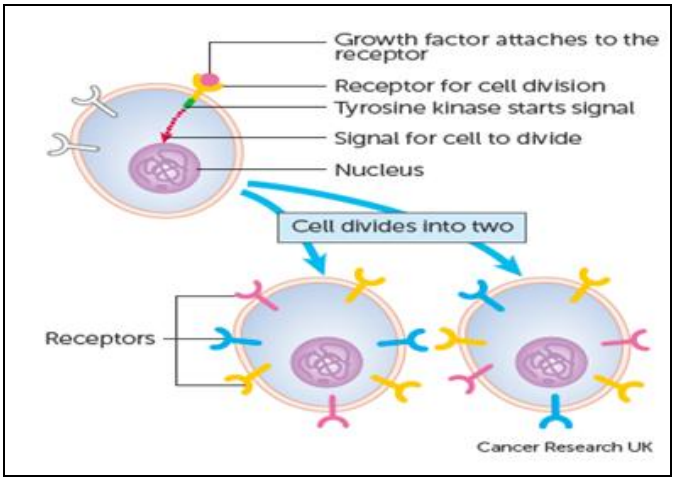

FIG. 1: MECHANISM OF GROWTH FACTOR

QUICK RESPONSE CODE

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Mammalian Target of Rapamycin Inhibitors (mTORIs), Phosphoinositide 3-Kinase Inhibitors (PI3KIs), Histone Deacetylase Inhibitors (HDACIs), Hedgehog Pathway Inhibitors (HPIs)] which are used for blocking the function of growth factors [1].Generally, tyrosine kinases are the protein kinases which activate the proteins by undergoing phosphorylation with the phosphate group (ATP) of growth factors and affects the apoptosis, proliferation, and differentiation of cells in living organisms [2]. These TKIs inhibits the action of tyrosine kinase enzyme by preventing the phosphorylation. Then the transferring of signals from one cell to another cell decreases thereby preventing the proliferation of malignant cancer cells **Fig. 2** [2, 3]. Examples of TKIs are listed in **Table 1.** In recent years multiple TKIs are approved for the treatment of cancers [4]. The main aim of the present review is to estimate various TKIs by using different analytical instruments such as LC-MS, UPLC, HPTLC, HPLC, Spectrofluorimetry, UV-Visible spectrophotometry, *etc*., in pharmaceutical and last decade [5, 9,] reported in the literature within the last decade. This review summarises the up-to-date analytical-based strategies in TKIs analysis and discusses the challenges and opportunities in this rapidly evolving field.

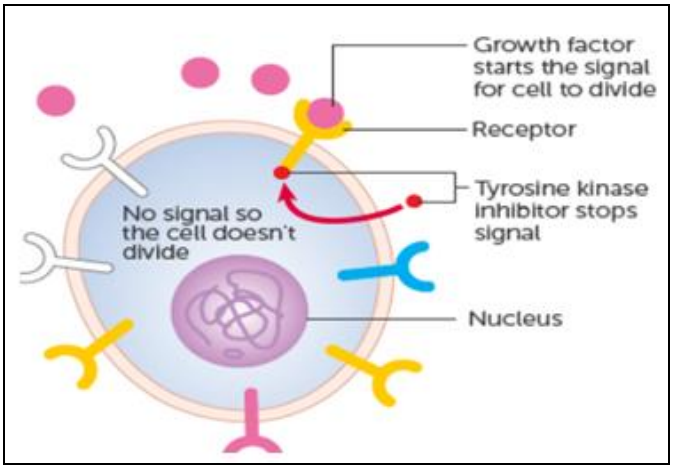

FIG. 2: MECHANISM OF TYROSINE KINASE INHIBITORS

TABLE 1: LIST OF THE TYROSINE KINASE INHIBITOR'S

S. no.	TKIs	S. no.	TKIs	S. no.	TKIs
1	Imatinib	16	Tandutinib	31	Fedratinib
2	Sunitinib	17	Nilotinib	32	Vemurafenib
3	Dasatinib	18	Erlotinib	33	Sorafenib
4	Flumatinib	19	Ibrutinib	34	Pazopanib
5	Genistein	20	Gefitinib	35	Lapatinib
6	Acalabrutinib	21	Ponatinib	36	Dovitinib
7	Lestaurtinib	22	Saracatinib	37	Alectinib
8	Midostaurin	23	Osimertinib	38	Regorafenib
9	Vatalanib	24	Dacomitinib	39	Gilteritinib
10	Motesanib	25	Crizotinib	40	Lenvatinib
11	Cabozantinib	26	Vandetinib	41	Olmutinib
12	Axitinib	27	Bosutinib	42	Entrectinib
13	Tucatinib	28	Nintedanib	43	Erdafitinib
14	Selumetinib	29	Fostamatinib	44	Ruxolitinib
15	Selpercatinib	30	Foretinib	45	Pexidartinib

LC-MS/MS Methods: Liquid chromatography (LC) is a separation technique that separates the sample components in a mixture based on their polarity and affinity of components. Then, it introduces these separated components into the mass spectrometer (MS) to detect and separate the components based on their m/z ratio. This data is used to provide information about the molecular weight, identity, and quantity of specific sample components [10]. Numerous liquid chromatographic methods have been reported for the analysis of various TKIs in bulk and pharmaceutical dosage forms and biological matrices. Ramarao NT *et al.*, [11] developed a simple, rapid, and specific LC-MS/MS method for the estimation of erlotinib in human plasma and erlotinib D6 used as an internal standard. The separation was carried out on Phenomenex Luna C18 analytical column (50 × 1 mm, 5 µ) with the temperature of 40 °C with the mobile phase consisting of acetonitrile and 10 mM ammonium formate buffer (80:20% v/v) with isocratic mode at a flow rate of 0.5 mL/min. The runtime for each sample is 3.5 min. A positive electrospray ionization mode was used for the

sample analysis. Bobin-Dubigeon C *et al.,* [12] introduced a rapid and sensitive method for the determination of sorafenib in human plasma. The analysis was performed on pursuit XRS ultra column (100 × 2 mm, 2.8 µ) using an isocratic flow with a mobile phase consisting of 0.1% formic acid and acetonitrile (80:20% v/v) at a flow rate of 0.3 mL/min. Mass spectrometry in the single-ion monitoring mode was used for the detection. Sample analysis was carried out on positive electrospray ionization mode, and it was operated at 350 °C.

A reliable, fast liquid chromatography-tandem mass spectrometric method was proposed by Attwa1 MW *et al.,* [13] for the quantification of foretinib in plasma, urine, and rat liver microsome samples. Brigatinib was used as an internal standard for the analysis of foretinib separation was achieved on Eclipse C18 analytical column (50 × 2.1 mm, 1.8 µ) with the temperature of 22 ± 1 °C. The mobile phase consists of 60% ammonium formate (10 mM, pH 4.2) and 40% acetonitrile with isocratic mode. Chromatographic peaks were resolved with 0.25 mL/min flow rate. The run time for each sample was 3 min. A positive electrospray ionization mode was used for the sample analysis. Agilent Mass Hunter software was used to control instruments and data acquisition.

Hepsebah NJR *et al.,* [14] developed and validated a fast and highly sensitive bio analytical LC-MS/MS technique for the quantification of ibrutinib in human plasma by using internal standard ibrutinib-D5. Chromatography was accomplished on C18 column (75×4.6 mm, 3.5 µ) by acetonitrile, methanol and 0.1 %v/v formic acid as the mobile phase with gradient elution. Elution of analytes was carried out using a flow rate of 0.7 mL/min and the total run time is 6 min. The sample analysis was performed by electro-spray ionization with positive mode. Shan xiong *et al.,* [15] reported a novel liquid chromatographic method for the determination of osimertinib in rat plasma. Chromatography was achieved on Hypersil GOLD C18 analytical column (50 × 2.1 mm, 3 µ) with a temperature of 25 °C. The elution was carried out by using acetonitrile and water containing 0.1% formic acid as a mobile phase with gradient elution. The total run time was 2.5 min. flow rate was 0.4 mL/min. A positive ESI mode was used for the sample analysis. Thermo-scientific software was used for the data analysis. Abdelhameed AS *et al.,* [16] developed and validated an LC-MS/MS assay method for the estimation of dacomitinib in rat liver microsomes where lapatinib was used as an internal standard. The chromatographic separation was carried out on agilent eclipse plus C18 analytical column (100 × 2.1 mm, 1.8 µ) with isocratic elution by acetonitrile and ammonium formate (adjust the pH to 4.2 using formic acid is used as mobile phase. The column temperature was maintained at 22 ± 1 °C. The runtime was 4 min. Data analysis was performed by using mass hunter software. Detection was carried out by using a triple quadrupole mass detector operated with ESI positive ionization mode.

Kadi AA *et al.,* [17] proposed a method for the quantification of ponatinib in human plasma and rat liver microsome where vandetanib is used as an internal standard. Chromatographic separation was achieved on agilent eclipse plus C18 column (50 × 2.1 mm, 1.8 µ) with column temperature at 21 ± 2 °C. The chromatographic peaks were resolved by the mobile phase consisting of 10 mM ammonium formate (solvent A) having pH of 4.1 by addition of formic acid and acetonitrile (solvent B) with a flow rate of 0.25 mL/min. Injection volume was 5 µL with a total run time of 4 min. A triple quadrupole mass spectrometer with electrospray ionization source interface running in the positive mode was used for detection. Data were recorded, and the system was controlled using Mass Hunter software.

Ling-Zhi Wanga *et al.,* [18] developed a new liquid chromatographic method and validated for the estimation of gefitinib in human plasma. O-desmethyl gefitinib-d3 was used as an internal standard. The elution of the analyte was achieved on Alltech Alltima C18 analytical column (150 × 2.1 mm, 5 µ) with a temperature of 20 °C. Acetonitrile and 0.1% formic acid in water (30:70% v/v) were used as mobile phase in isocratic mode. The flow rate was 300 µL/min, and the injection volume was 10 µL with a run time 3 min. API4000 (atmospheric pressure ionization) was used for the detection with a triple quadrupole mass spectrometer. Rolf W *et al.,* [19] introduced a bioanalytical method and validated for the quantitative estimation of crizotinib in mouse plasma. In this method Acquity UPLC BEH C18

column (30 × 2.1 mm, 1.7 µ) with 40 °C was used for the separation. 0.1% v/v of ammonium hydroxide (A) and methanol (B) was used as mobile phase with a flow rate of 0.6 mL/min by gradient mode. 2.5 min is the run time for each sample. The analyte was detected by using a triple quadrupole mass spectrometer with positive ESI mode. Data analysis was carried out by using Thermo Fisher Scientific Xcalibur software. A simple and sensitive LC-MS/MS method was proposed by Srikanth I *et al.,* [20] for the determination of cabozantinib in human plasma. Cabozantinib-d4 was used as an internal standard. The elution of analyte was carried out on Xbridge C18 analytical column (50 × 4.6 mm, 5 µ) with 40 °C. The mobile phase used was 10 mM ammonium formate and methanol in the ratio of 20:80% v/v with the isocratic mode at a flow rate of 0.7 mL/min. The run time for each sample was 3 min. The analyte was detected by using turbo ion spray positive mode. The validation parameters of LC-MS/MS methods were mentioned in **Table 2.**

TABLE 2: VALIDATION PARAMETERS REPORTED FOR LC-MS

Drugs	Parameters							
	Linear range (ng/mL)	**Correlation coefficient (r^2)**	**% Recovery (Accuracy)**	**Precision Interday (% RSD)**	**Precision Intraday (% RSD)**	**Limit of Detection (ng/mL)**	**Limit of Quantification (ng/mL)**	**% Assay**
Erlotinib [11]	10-5,000	0.99895	98.47-102.48	5.24	5.24	-	10 (LLOQ)	-
Sorafenib [12]	10-10,000	0.993	92.2	7.3	6.5	5 ng/mL	10	-
Foretinib [13]	5-500	0.9993	98.8 (-1.24)	1.21-1.67	0.16-1.24	1.8	6.0	-
Ibrutinib [14]	1-600	> 0.99	99.28-102.8	2.9-6.1	2.5-8.1	-	1 (LLOQ)	-
Osimertinib [15]	1.0-1000	0.9960	92.66-101.5 (intra-day) 97.08-99.15 (inter day)	3.43 - 10.44	6.25-10.34	-	1 (LLOQ)	-
Dacomitinib [16]	2-500	0.9989	92.20-100.32	1.08-3.58	0.84-1.26	0.35	1.1	-
Ponatinib [17]	5-400	≥ 0.9998	-	-	-	1.53 (in plasma) 1.38 (in RLM)	4.66 (in plasma) 4.19 (in RLM)	-
Gefitinib [18]	5-1000	0.9998	89.7-104.7	≤ 10.8	≤ 10.8	-	5 (LLOQ)	
Crizotinib [19]	10-10,000	0.99980±0.0 0014	107-112	3.6-4.9	3.4-4.8		9.49±0.41 (LLOQ)	
Cabozantinib [20]	5.0-5000 pg/mL	≥ 0.9994	97.92-102.2	2.93-9.3	1.95-2.37	50 pg/10 µL	5 pg/mL	

UPLC-MS/MS Methods: UPLC is the new version of HPLC which can separate the small particle-sized components, *i.e.,* lesser than 2 µm. It has the ability to withstand high system backpressure and can improve resolution, speed, and sensitivity [21]. A simple and accurate method was developed by Wani TA *et al.,* [21] for the estimation of crizotinib in human plasma by using the sensitive UPLC-MS/MS method. In order to separate crizotinib from paroxetine, an internal standard performed protein precipitation method using 50:50 acetonitrile and methanol as solvent. C18 column (50 × 2.1 mm, 1.7 µ) was used for separation of analytes and methanol: 0.1% ammonium hydroxide at the ratio of 80:20 was used as mobile phase with 0.4 mL/min flow rate and the total run time 2 min. Here the UPLC-MS/MS system was controlled by Mass Lynx software. Ezzeldin E *et al.,* [22] proposed a new method for the estimation of foretinib by using UPLC-MS/MS in animal plasma. An Acquity BEH C18 column (100 × 2.1 mm, 1.7 µ) was used for foretinib separation. The maximum concentration of foretinib was observed at 4 hr after the single-dose administration. Zhen Yang *et al.,* [23] described a sensitive and reproducible UPLC-MS/MS method for the simultaneous estimation of genistein and its four phase-II metabolites, i.e., Genistein-7-O-glucuronide (G-7-G), genistein-4′-O-glucuronide (G-4-G), genistein-4-O′-sulfate (G-4′-S), and genistein-7-O-sulfate (G-7-S) in mouse blood samples. In this internal standard used was Daidzein. A mixture of 100 % aqueous buffer (pH 7.4) (A) and 100% acetonitrile (B) used as mobile

phase by gradient elution at a flow rate of 0.45 mL/min, and the column used was Acquity UPLC BEH C18 column (50 × 2.1 mm, 1.7 µ). A simple and sensitive quantitative UPLC-MS/MS analytical method was introduced by Xin Zheng *et al.,* [24] for the determination of osimertinib and its metabolites in human plasma by using BEH C18 column (50 × 2.1 mm, 1.7 µ) at 35 °C and 0.1% v/v formic acid and 10 mM ammonium acetate in water and acetonitrile used as a mobile phase on gradient mode with flow rate 0.4 mL/min and the total run time of each sample is 3 min.Dan Lin *et al.,* [25] developed a new method for the simultaneous determination of nintedanib and its metabolites by UPLC-MS/MS in rat plasma using Acquity BEH C18 column (50 × 2.1 mm, 1.7 µ) with gradient elution containing mobile phase A as acetonitrile and mobile phase B as 0.1% formic acid. The flow rate was kept at 0.3 mL/min, and the total run time was 3 min. A simple and accurate UHPLC-MS/MS method was developed by Su-su Bao *et al.,* [26] for the quantitation of olmutinib in rat plasma using C18 RRHD (50 × 2.1 mm, 1.8 µ) column and a mobile phase of 0.1% formic acid in water and acetonitrile on gradient mode with flow rate 0.4 mL/min and the total runtime was 1.7 min for each sample.

Xiangjun Qiu *et al.,* [27] introduced a simple bioanalytical assay for the estimation of dacomitinib in rat plasma by UPLC-MS/MS using Acquity BEH C18 column (50 × 2.1 mm, 1.7 µ) at 40 °C containing mobile phase with solvent A as acetonitrile and solvent B as 0.1 % formic acid in water on gradient mode with a flow rate of 0.4 mL/min.

TABLE 3: VALIDATION PARAMETERS REPORTED FOR UPLC-MS/MS AND UPLC

Parameters	Results						
	Linear range	Correlation coefficient (r^2)	Accuracy (% Mean recovery)	Precision Interday (% RSD)	Precision Intraday (% RSD)	Limit of Detection (µg/mL)	Limit of Quantification (µg/mL)
Crizotinib [21]	5-500 ng/mL	0.9986	102.6±2.02 (Inter-day) 102.1±1.98 (Intra-day)	0.7-2.3	1.9-11.0	1.80 ng/mL	5 ng/mL (LLOQ)
Foretinib [22]	0.5-400 ng/mL	0.9982	86.7-92.0 (Inter-day) 87.0-92.0 (Intra-day)	3.1-10.9	4.9-10.6	-	0.5 ng/mL (LLOQ)
Genistein [23]	19.5-10000 nM	-	92.5-110.8 (Intra-day)	3.0-5.8	5.9-8.2	-	4.88(LLOQ)
Osimertinib [24]	0.5-100 ng/mL	0.9947	93.7-116.5	11.4	9.6	-	0.417-0.482 (LLOQ)
Nintedanib [25]	1.0-200 ng/mL	0.9906	-11.9-10.4	3.5-10.2	3.1-9.0	-	1.0 ng/mL
Olmutinib [26]	1-500 ng/mL	0.999	85.8-95.5	1.4-5.8	1.8-10.0	-	-
Dacomitinib [27]	1-150 ng/mL	0.9953	76.9-84.1	2.2-8.7	1.7-8.4	-	1 ng/mL
Cabozantinib [28]	20-120 µg/mL	0.9997	99.57-99.91	0.4	0.3	0.15	0.47
Dasatinib [29]	0.5-50 µg/mL	0.9999	103.96-105.95	0.23-0.43	0.18-0.29	0.006	0.019
Lapatinib [30]	10-50 µg/mL	0.999	99.69	-	0.7	0.06	0.18

UPLC Methods: From the literature survey, identified several methods had been published for the determination of various TKI's using Ultra Performance Liquid Chromatography (UPLC). G. Ashok *et al.,* [28] introduced a simple and accurate stability-indicating method for the estimation of cabozantinib in capsule dosage form at 244 nm by using UPLC. The column used is C18 (100 × 2.1 mm, 1.7 µ) at 30 °C using 0.1% ortho-phosphoric acid and acetonitrile in the ratio of 55:45% v/v mobile phase on isocratic mode with 0.3 mL/min as flow rate and the total run time was 3 min. They also performed forced degradation studies by exposing the drug to various stress conditions like acidic, basic, peroxide, neutral, photolytic, and thermal degradation studies. Gonzalez AG *et al.,* [29]

developed a simultaneous UPLC and capillary zone electrophoresis method for the estimation of dasatinib in tablet dosage form by using Acquity UPLC BEH C18 (100 × 2.1 mm, 1.7 µ) column with methanol and acetonitrile as mobile phase on isocratic elution mode with flow rate 0.3 mL/min and the total run time is 2 min. A new simple and rapid UPLC method was developed for estimation of lapatinib in pharmaceutical tablet dosage form at 309 nm and validated according to ICH guidelines using PDA detector by Biswal S *et al.,* [30].

The chromatographic separation was done using BHEL UPLC Column. The mobile phase used was a mixture of 0.1% orthophosphoric acid buffer: Acetonitrile at a ratio of (30:70% v/v) at isocratic mode with a flow rate of 0.25 mL/min. The validation parameters of UPLC-MS/MS and UPLC methods were mentioned in **Table 3.**

HPLC Methods: HPLC is a type of liquid chromatography that can separate the components in a mixture based on their polarity and affinity towards the stationary phase [31]. There are numerous HPLC methods have been reported for the estimation of TKIs in bulk and dosage forms as well as biological matrices using various detectors like UV, PDA, *etc.* Arun Kumar K *et al.,* [32] developed a validated method for the estimation of ceritinib in pharmaceutical formulation by RP-HPLC. The elution was achieved on Kromosil C18 (250 × 4.6 mm, 5 µ) with mobile phase containing buffer and acetonitrile in the ratio of 40:60% v/v, at a flow rate of 1.0 mL/min, and detection was carried out at 320 nm. The retention time for ceritinib was 2.337 min. The linearity was obtained in the range of 25-150 µg/mL. The injection volume and total run time were 10 µL and 6.0 min, respectively. Here correlation coefficient (r2) was 0.9992. Chromatographic data were obtained by empower 2 software.

Ananda T *et al.,* [33] introduced a method for estimation of erlotinib in pharmaceutical dosage form by using the RP-HPLC instrument. Chromatographic separation was achieved on the isocratic mode by using a reverse-phase Merck C18 analytical column (250 × 4.6 mm, 5 µ) with a temperature of 27 °C. The mobile phase consists of potassium dihydrogen orthophosphate and acetonitrile (70:30% v/v) with pH 5.0 (adjusted with orthophosphoric acid) with a flow rate of 0.8 mL/min. The injection volume was 20 µL. The UV detection wavelength selected was 246 nm. The retention time of erlotinib was 4.54 min.

Prem Kumar B *et al.,* [34] proposed and validated the method for assay of crizotinib in bulk and pharmaceutical dosage form by RP-HPLC. The chromatographic separation was achieved on inertsil BDS (250 × 4.6 mm, 5 µ) analytical column with isocratic mode, and the column temperature was adjusted to 30 °C. Mobile phase consists of buffer and acetonitrile in the ratio of 60:40%v/v with the flow rate of 1 mL/min, and eluent was monitored at 267 nm with PDA detector. Total run time was 30 min. The injection volume was 20 µL.

Sonal SF *et al.,* [35] developed a method for the assay of bosutinib in bulk and pharmaceutical dosage form by RP-HPLC. Elution was carried out by using C18 analytical column (250 × 4.6 mm, 5 µ) with isocratic mode and acetonitrile: methanol: water (80:5:15) used as a mobile phase and the flow rate was 1.0 mL/min. Eluent was monitored at 246 nm after injecting 10 µL samples. Retention time for bosutinib was 5.63 min. Sureshbabu K *et al.,* [36] developed and validated a stability-indicating RP-HPLC method for the estimation of ibrutinib in pharmaceutical dosage form at 320 nm. The chromatographic separation was conducted on Waters HPLC 2695 series system with inertsil ODS (100 × 4.6 mm, 5 µ) analytical column with the temperature of 30 °C. 0.1% orthophosphoric acid buffer and acetonitrile in the ratio of 70:30% v/v was used as a mobile phase by isocratic mode at a flow rate of 0.8 mL/min and 20 µL was injected.

Harika M *et al.,* [37] developed a method for estimating nilotinib by using RP-HPLC in bulk and pharmaceutical dosage form. The separation of analyte was carried out on C18 analytical column (250 × 4.6 mm, 5 µ) with isocratic mode. The mobile phase consists of water and acetonitrile (50:50% v/v) with the flow rate of 1.0 mL/min. Here PDA detector was used at 254 nm. The retention time for nilotinib was 3.874 min. The linearity of drug was obtained in the concentration range of 5-250 µg/mL with the correlation coefficient of 0.999. The run time was 6 min and injection volume 20 µL. The developed method was validated as per ICH guidelines. Puja P *et al.,*

[38] proposed a method for the estimation of pexidartinib in the pharmaceutical dosage form. The elution was carried out on C18 analytical (250 × 4.6 mm, 5 µ) column with isocratic mode. The mobile phase consists of phosphate buffer (pH 4.5 adjusted with 1% orthophosphoric acid) and acetonitrile (75:25 %v/v) at a flow rate of 1 mL/min. UV detection was carried out at 233 nm. The retention time of the analyte was 7.237 min. Linearity was obtained in the concentration range 10-30 µg/mL and injection volume 20 µL. Nagoji KEV *et al.*, [39] introduced an RP-HPLC method for the estimation of lapatinib in tablet dosage form at 232 nm and the internal standard used is gemcitabine HCl. The method was optimized on an ODS C18 analytical column (250 × 4.6 mm, 5 µ) with gradient mode. The mobile phase used was acetonitrile and water with 50:50% v/v at a flow rate of 1.0 mL/min with run time 8 min, and the injection volume was 20 µL. The linearity of drug was obtained in the concentration range of 2-60 µg/mL.

TABLE 4: VALIDATION PARAMETERS REPORTED FOR HPLC METHODS

Drugs	Parameters							
	Linear range (µg/mL)	**Correlation coefficient (r^2)**	**% Recovery**	**Precision Interday (% RSD)**	**Precision Intraday (% RSD)**	**Limit of Detection (µg/mL)**	**Limit of Quantification (µg/mL)**	**% Assay**
Ceritinib [32]	25-150	0.9992	100.31	0.57	0.80	2.335	2.340	99.40
Erlotinib [33]	10-60	0.999	98.69-101.97	0.1971	0.2099	0.62	2.07	99.5
Crizotinib [34]	25-150	0.999	100.25-101.2	0.93	1.26	0.080	0.243	100.24
Bosutinib [35]	20-100	0.999	99.83-100.18	0.00790-0.12164	0.00829-0.09462	0.00062	0.001879	-
Ibrutinib [36]	3.5-21.0	0.9997	100.33-100.90	1.7252	1.0583	0.03	0.10	-
Nilotinib [37]	5-250	0.999	99.37-100.21	0.49-1.20	0.288-0.99	0.26	0.79	98.92
Pexidartinib [38]	10-30	0.9999	98.43-101.13	0.66-1.64	0.41-1.95	0.25	0.82	99.55
Lapatinib [39]	2-60	0.996408	95.90-104.53	0.128-0.289	0.128-0.289	0.265	0.884	99.98
Gefitinib [40]	25-300	0.9999	99.79-99.92	0.25	0.25	0.125	0.375	99.5
Dasatinib [41]	2-10	0.999	98.09-99.93	0.0016	0.0022	0.5263	1.5948	99.45
Imatinib [42]	10-50	0.999	98.42-100.4	0.20-1.30	0.43-1.24	0.5227	1.5842	99.13
Sorafenib [43]	5-80	0.998	99.95-100.23	0.5998	0.2975	0.133	0.403	99.98
Pazopanib [44]	5-45	0.9998	98.8- 99.2	0.06	0.28	0.05	0.1	-

Kiran Kumar V *et al.*, [40] developed a method for the estimation of gefitinib in tablet dosage forms by RP-HPLC at 246 nm. The separation process was carried out by using Hypersil BDS reverse phase C18 analytical column (250 × 4.6 mm, 5 µ). 0.02 M dipotassium hydrogen orthophosphate and methanol in the ratio of 10:90% v/v was used as mobile phase with the flow rate of 1.0 mL/min with run time 8 min and the retention time was 3.7 min. Injection volume was 20 µL. The linearity of drug was 25-300 g/mL. Ravi Sankar P *et al.*, [41] proposed a method for the estimation of dasatinib in tablet dosage form by using the RP-HPLC technique at 323 nm. Elution was carried out on agilent-1260 series with C18 column (250 × 4.6 mm, 5 µ) with isocratic mode. HPLC grade methanol and acetonitrile in the ratio of 50:50% v/v was used as mobile phase at a flow rate of 1 mL/min with a retention time of 4.073 min and run time was 8 min. The linearity concentration range is 2-10 µg/mL. Suwarna BP *et al.*, [42] developed and validated a method for the estimation of imatinib mesylate in pure and pharmaceutical dosage form by RP-HPLC at 264 nm. The chromatography was carried out on C18 analytical column (250 × 4.6 mm, 5 µ) with isocratic mode. The mobile phase

used was acetonitrile, orthophosphoric acid (0.1%) in the ratio of 60:40% v/v at isocratic mode with a flow rate of 1.0 mL/min. The retention time for imatinib was found to be 6.08 min, and the run time was 5 min. The linearity was 10-50 µg/mL. Kalaichelvi R *et al.,* [43] proposed a method for estimation of sorafenib tosylate in its pure form and in its tablet formulation by RP-HPLC method. Separation of compounds was achieved on Phenomenex Luna C18 analytical column (250 × 4.6 mm, 5 µ). The mobile phase used was acetonitrile and water in the ratio of 82.5:17.5% v/v at isocratic mode with a 1.5 mL/min flow rate. The linearity of the drug was obtained in the concentration range of 5-80 µg/mL. Detection was carried out by UV detector at 265 nm. Data analysis was performed by using LC solutions software. Kishore Kumar Reddy Y *et al.,* [44] proposed a method for the estimation of pazopanib in bulk and its dosage form. Elution was carried out by using Phenomenox Kinetex-C18 analytical (100 × 4.6 mm, 5 µ) column with a temperature of 40 °C. The isocratic mobile phase consists of potassium dihydrogen phosphate buffer and methanol in the ratio of 60:40 (v/v) with flow rate 0.8 mL/min and detection was monitored at 263 nm by UV detector. Data analysis was performed by empower 3 software. The validation parameters of HPLC methods were mentioned in **Table 4.**

HPTLC Methods: HPTLC is an automatic and sophisticated technique that TLC which can able to separate smaller particle sizes less than 5 µm based on their affinity towards the adsorbent. This method is also known as planar chromatography or flat bed chromatography [45]. The literature survey stated that various methods had been published for the determination of various TKI's using High-Performance Thin Layer Chromatography (HPTLC). Ritesh B *et al.,* [46] developed a simple stability-indicating HPTLC method for the estimation of Dasatinib at 240 nm. Here mobile phase used was toluene: methanol (6:4% v/v), and the stationary phase was Silica G60 F254 pre-coated TLC plates. The R_f value of dasatinib was found to be 0.65 ± 0.03. They also performed stability-indicating studies in an alkaline medium, and its degradation products are separated and isolated by HPTLC and identified by using the MS-MS technique.

TABLE 5: VALIDATION PARAMETERS REPORTED FOR HPTLC

Parameter	Results		
	Dasatinib [46]	**Genistein [47]**	**Sunitinib [48]**
Linear range	200-1200 (ng/band)	100-600 (ng/band)	27.34-437.5 (ng/spot)
Correlation coefficient (r^2)	0.995	0.9978	0.9971
% Recovery	99.8-100.8	99.96	93.53-100.88
Precision Interday (% RSD)	4690.82-4991.44	0.54-0.87	2.63
Precision Intraday(% RSD)	4489.26-4603.62	0.46-1.01	0.75
Limit of Detection (µg/mL)	0.92	14.786	23.26
Limit of Quantification (µg/mL)	2.817	44.805	70.50
Slope	1168.7	6.424	4.0191

A simple and accurate high-performance thin layer chromatography densitometry method was developed by Swaha S *et al.,* [47] for the simultaneous estimation of genistein and daidzein in ethanolic extract of Pueraria tuberose (Vidarikanda), and its various fractions are studied at 269 nm. Here mobile phase used was toluene: ethyl acetate: acetone: formic acid (20:4:2:1), and stationary phase is Silica G60 F254 with 0.2 mm thickness.

The R_f value of genistein and daidzein was found to be 0.54 ± 0.02 and 0.39 ± 0.02, respectively. Hajmalek M *et al.,* [48] introduced a simple HPTLC method for the estimation of sunitinb malate and possible impurities by using densitometry at 430 nm. They performed the chromatographic separations using 20 × 20 cm aluminum-backed plates pre-coated with kieselguhar 60F-254. Different compositions of solvent systems were tested from which the selected optimized mobile phase was a mixture of dichloromethane: methanol (3:1% v/v) for the separation of the two stereoisomeric forms of sunitinib malate. Impurities present in sunitinb such as E-isomer, impurity-B, Sunitinib N-oxide are separated based on the R_f value 0.35 ± 0.02 of Sunitinib. The validation parameters of HPTLC methods were mentioned in **Table 5.**

Spectrofluorimetric Methods: Spectrofluorimetry is the analytical tool used to separate the components in a mixture based on the fluorescence nature [49]. From the literature survey identified, several methods have been published for the determination of various TKI's using spectrofluorimetry. Darwish HW *et al.,* [50] developed a simple and sensitive micelle enhanced spectrofluorimetric method for the determination of cabozantinib in pharmaceutical formulation and spiked human plasma. This method deals with the fluorescence spectral behavior of cabozantinib at λem 343nm and λex 244 nm in cremophor RH 40 micellar system. The % recovery values obtained for the cabozantinib were 99.68±0.88, 100.53 ± 0.51, and 100.44 ± 3.91% for pure powder, lab-prepared dosage form, and spiked human plasma, respectively. Darwish HW *et al.,* [51] described a simple and sensitive spectrofluorimetric method for the determination of dasatinib at 300-450 nm in tablet formulation and spiked human plasma and urine using cremophor EL micellar system using synchronous scan technique (Δλ = 50 nm). This method is also helpful for the estimation of in vitro drug release of dasatinib tablets. The % recovery values obtained for dasatinib were 100.18, 98.47, 91.98, and 100.52 for a pure form, tablet (Sprycel) formulation, plasma sample, and urine sample respectively. A new simple and sensitive spectrofluorimetric method was developed by Darwish HW *et al.,* [52] to determine vandetanib in tablets, plasma, and urine. This method was based on the intrinsic fluorescence intensity of vandetanib in acetonitrile at em 480 nm and ex 330 nm. The % recovery values obtained for vandetanib were 100.92, 97.86, 97.97, and 97.59 for the pure form, tablet formulation, plasma, and urine sample respectively. The validation parameters of spectrofluorimetry methods were mentioned in **Table 6.**

TABLE 6: VALIDATION PARAMETERS REPORTED FOR SPECTROFLUORIMETRY

Parameter	Results		
	Cabozantinib [50]	Dasatinib [51]	Vandetanib [52]
Linear range (ng/mL)	25-800	25-500	20-600
Correlation coefficient (r^2)	0.9991	0.9998	0.997
S.D of slope	0.028	1.372	0.009
Precision Interday (% RSD)	99.875	101.59	97.765
Precision Intraday(% RSD)	99.385	100.70	99.905
Limit of Detection (ng/mL)	13.4	2.70	10.05
Limit of Quantification (ng/mL)	20	8.17	30.45
S.D of intercept	7.404	0.005	2.711

Spectrophotometric Methods: It is a technique that measures the intensity of light at a certain range of wavelength *i.e.,* 200-400 nm. It majorly depends on the absorbing capacity of components in sample [53]. From the literature survey, identified several methods had been published for the determination of various TKI's using UV-Visible spectrophotometry. Ravisankar P *et al.,* [53] developed simple stability indicating UV-spectrophotometric method for the determination of dasatinib in bulk and tablet dosage form with max 323 nm in methanol and acetonitrile (50:50) as solvent.

They performed degradation studies which showed that there is no degradation in photolytic and alkaline medium, slight degradation in acidic medium, extensive degradation by oxidation, and complete degradation was observed in thermal degradation. Isabela da Costa Cesa *et al.,* [54] developed and validated UV-Visible spectrophotometric method for quantification of genistein and its glycoside genistin in soy dry extract after reacting with $AlCl_3$. There are other isoflavones like daidzein and glycitein where it cannot be evaluated at 382 nm. So it is a simple and accurate method for the estimation of genistein. Chaitanya G *et al.,* [55] introduced a novel method for the determination of pazopanib hydrochloride in bulk and tablet dosage form by using UV-Visible double beam spectrophotometric method at 214 ± 0.2 nm. They validated various parameters like accuracy linearity, precision, LOD, LOQ as per ICH guidelines.

A simple, accurate UV-Visible double beam spectrophotometric method was developed by Jadhav PB *et al.,* [56] for the estimation of bosutinib in bulk and tablet dosage form. A simple, precise UV-Visible double beam spectrophotometer was

introduced by Chaitanya G *et al.,* [57] for the determination of nilotinib hydrochloride in bulk and capsule dosage form at 263 ± 0.2 nm. The validated parameters are mentioned in **Table 7** for the estimation of TKIs by UV-Visible spectrophotometry.

TABLE 7: VALIDATION PARAMETERS REPORTED FOR UV-VISIBLE SPECTROPHOTOMETRY

Parameter	Result				
	Dasatinib [53]	**Genistein [54]**	**Pazopanib [55]**	**Bosutinib [56]**	**Nilotinib [57]**
Linear range (µg/mL)	2 – 10	2 – 12	5.5 - 7.5	5 – 30	7 – 12
Correlation coefficient (r^2)	0.999	0.9999	0.9933	0.9994	0.9984
Accuracy (% Meanrecovery)	100.01	99.69±0.873	99.69	101.36	100.05±0.421
Precision Interday (% RSD)	0.0245 - 0.0512	1.16 %	0.33	0.04 - 0.1	0.37
Precision Intraday (% RSD)	0.0245 - 0.0512	0.65 %	0.23	0.017 - 1.3	0.16
Limit of Detection (µg/mL)	0.3968	0.25	0.24	0.25	0.28
Limit of Quantification (µg/mL)	1.2025	0.76	0.75	0.76	0.85
% Assay of pure drug	100.0645 ± 0.0002	-	-	100.5	-
% Assay of tablet formulation	99.8870 ± 0.0002	-	99.44	-	99.20

CONCLUSION: The information provided by chromatography and spectroscopy are very different and orthogonal techniques. HPLC technique is used for separation, identification and quantification of components either alone or a mixture suitable for which are not easily volatilized, thermally unstable with high molecular weights. The GC is effective in the analysis of mixture of gases or liquids having low boiling points. Also, chromatography is applied to separate thermally labile liquid mixtures or have high boiling points.

The UV method has an advantage over HPLC because it does not require the elaborate procedure usually in the chromatographic method and UV method is less time-consuming and economical. Hence the HPLC and UV spectroscopy are important methods to quantify a drug in pure and dosage form. The accelerated development of new methods are required for TKIs hence, chromatography-mass spectrometry is applied to quantification either alone or combination of TKIs in a range of pharmaceuticals. For this purpose, some new extraction methods are also employed for the study of complex samples without interferences from the matrix at very low concentrations.

Amongst chromatographic methods, LC-MS, LC-MS/MS, GC-MS, and GC-MS/MS are the most widely used techniques for determining TKIs investigated. Among these techniques, LC-MS/MS methods have the advantages of less complicated sample preparation and versatility to analyze a large number of TKIs in a single run. The use of pre-extraction and pre-concentration sample preparation steps, such as solid-phase extraction, is important for high linear range analytical methods. But the ultimate choice of method will depend on prevailing circumstances in the laboratory and the clinical situations in which the assay is to be used. Hence researchers are focused on developing simple, easy, and cost-effective methods for quantifying various TKIs in pure, formulations and biological matrices. Therefore, this review will help researchers widen their ideas on different improved aspects for further studies on the evaluation of the TKIs. The HPLC or LC-MS/MS or GC-MS/MS are time-consuming and labor-intensive. Due to such analytical limitations, alternative methodologies are warranted to analyze anti-cancer TKIs. Research on nanomaterial optical sensors based methods might lead us to a new horizon to overcome hurdles and develop alternative approaches.

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