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DASATINIB METHOD OF ANALYSIS: A REVIEW

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ABSRACT
Dasatinib is approved for the treatment of chonic myeloid leukaemia (CML). It is a kinase inhibitors. There are more than thirty methods have been reported for estimation of dasatinin in bulk, pharmaceutical formulations and biological fluids. This present review spotted different analytical methods such as chromatography, spectroscopy, hypenated techniques like LCMS, CZE, SLA studies of dasatinib. The current review uncovered that analytical and hypenated techniques that have been generally investigated and might help the analysts who are working with the analysis of dasatinib.

KEYWORDS: Dasatinib, Liquid Chromatography, Ultra-Violet spectroscopy, Mass spectroscopy.

INTRODUCTION

Cancer is viewed as one of the most frequent reasons for death in the advanced world and the number of diagnosed patients with different sorts of cancer is consistently expanding. Anticancer agents have been seriously evolved in the field of medicine.

Dasatinib is classified as a kinase inhibitor. Chemically it is N-(2-chloro-6 -methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5thiazole carboxamide, monohydrate. [1, 2] Chemical structure as shown in Fig. 1. Kinase inhibitors generally prevent the development of cancers by decreasing the activity of proteins that control cell division, development and endurance. Decrease of the protein action prompts concealment of the development and endurance of disease cells.[3]

It is a selective tyrosine kinase inhibitor used in the therapy of chronic myelogenous leukemia positive for Philadelphia chromosome.[4] Chronic myeloid leukemia is a hematopoietic stem cell disorder related with production of the Philadelphia chromosome due to mutual translocation between chromosomes 9 and 22 and results in the formation of chimeric protein called BCR-ABL which has an elevated tyrosine- kinase activity.[5]

General methods reported that are used in the analysis of Dasatinib. They are HPLC, HPTLC, UV Spectroscopy, Flourimetry, LC-MS, CZE which are summarized.

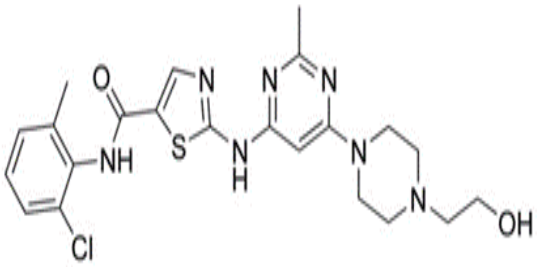

Fig 1: Structure of Dasatinib.

Ultra violet spectroscopy

Jyoti M et al developed a validated UV method for quantitative estimation of Dasatinib in bulk and pharmaceutical formulation. Acetonitrile was used as a solvent. The method showed as good reproducibility and recovery.[6]

Ravisankar P et al developed a UV method for determination of Dasatinib in bulk and pharmaceutical dosage form. Acetonitrile and Methanol used as solvent. The maximum absorbance was found to be 323 nm. Dasatinib was introduced to alkali, acid, oxidation, thermal, UV light degradation, it was more unstable in acidic, oxidation, thermal and stable in alkaline and ultra violet (UV) light irradiation. There were no UV methods have been reported with methanol and acetonitrile as solvent.[7]

Table 1: Reported UV methods for determination of Dasatinib.

S. No.	Detection wavelength	Solvent	Linearity range	LOD & LOQ	References
1	315nm	Acetonitrile	5-25µg/ml	LOD-0.908µg/ml LOQ - 2.752µg/ml	Jyoti M et al[6]
2	323 nm	Acetonitrile Methanol	2-10 µg/ml	LOD-0.3968 µg/ml LOQ-1.2025 µg/ml	Ravisankar P et al[7]

LOD - Limit Of Detection, LOQ - Limit Of Quantification.

Fluorimetry

Darwish HW et al. developed a spectroflourimetic method for determination of Dasatinib in pharmaceutical dosage form, spiked human plasma and urine samples. This method was very suitable to be applied for content uniformity testing. From the economical point of view, the method involved the native fluorescence property of Dasatinib, rather than expensive derivatizing analytical reagent.[8]

Table 2: Reported Flourimetry method for determination of Dasatinib.

S.No	Detection wavelength	Solvent	Linearity range	Recovery LOD LOQ	References
1	320nm(excitation) 370nm(emission)	Acetonotrile	25–500ng/ml	2.70ng/ml 8.17ng/ml	Darwish HW et al[8]

High Performance Thin Layer Chromatography

Bhole RP et al. developed a validated stability indicating HPTLC method using camag HPTLC system for estimation of Dasatinib in pharmaceutical dosage form. It could effectively separate the drugs from their degradation products and identified by using MS-MS technique.[9]

Mhaske DV et al. developed a stability indicating HPLC method for determination of Dasatinib in pharmaceutical dosage form. The drug was found to be stable in neutral, wet heat, dry heat and photodegradation conditions.[10]

Table 3: Reported HPTLC methods for determination of Dasatinib.

S. No.	Stationery phase Mobile phase	Detection wavelength	Retention factor (Rf) and Linearity	References
1	Silica G60 F254 precoated TLC plates, Toluene : methanol (6:4)	240nm	0.65 ± 0.03 Linearity– (200ng-1.2 µg/ml)	Bhole RP et al[9]
2	Silica gel 60 $F_{254,}$ Toluene:chloroform (7:3, *v/v*).	280nm	0.23 ± 0.02 Linearity- (500-6000 ng/ml)	Mhaske DV et al[10]

High Performance Liquid Chromatography (analytical)

Several HPLC method with different chromatogaphic conditions were described in table 4. The method developed by Elisa Pet al had higher sensitivity LOD10ng/mL(Imatinib), 10ng/mL(Dasatinib), 50ng/mL(Nilotinib)LOQ-50ng/mL(Imatinib),50ng/mL(Dasatinib),100ng/ml(Nilotinib) compared to the other methods.[17]

On the other hand Vani R et al developed a method that is economical because the mobile phase has 20% methanol and also the method has shorter run time (5 min) compared to other methods.[13]

Table 4: Reported HPLC (analytical) methods for determination of Dasatinib.

S.No	Stationary phase	Mobile phase	Flow rate and method of detection, Run time	Results	References
1	C-18 column (250 mm × 4.6 mm; 5 µm	Methanol: acetonitrile (50:50% v/v)	1.0 ml/ min UV at 232nm 8 min.	R_t – 4.073 min. Accuracy – 98.95%w/w LOD-0.5263 µg/ml LOQ-1.5948 µg/ml Linearity – (2-10 µg/ml)	Sankar PR et al[11]
2	Inertsil ODS C-18 column (150 mm x 4.6 mm; 5 µm)	Phosphate buffer : methanol(70:30 % v/v), pH=3	0.8 ml/min. PDA at 260nm 8 min.	R_t –2.5 min. (Dasatinib) 3.9 (Lenvatinib) Accuracy – 99.83 % (Dasatinib)	Junapudi S et al[12]

				100.15 % (Lenvatinib) LOD- 2.9 µg/ml(Dasatinib) 3.0µg/ml(Lenvatinib) LOQ- 10.3 µg/ml (Dasatinib) 10.01 µg/ml(Lenvatinb) Linearity- (100-500 µg/ml)Dasatinib, (1-5µg/ml) Lenvatinib	
3	Acquity CSH C-18 Column (150 mm X 2.0 mm; 1.5µm)	Tri ethylene amine: ACN: Methanol (30:50:20 % v/v)	1.0 ml/min. Uv at 230nm 5 min.	R_t -2.090min. Accuracy – 99.79% LOD- 8.74µg/ml LOQ- 26.50µg/ml Linearity- (50-250µg/ml)	Vani R et al[13]
4	Cosmicsil BDS C-18 (250 mm X 4.6 mm; 5µ)	A:B (50:50 v/v) triethylamine buffer, pH 6.5 ± 0.05 : methanol and Acetonitrile	1.0 ml/min. Uv at 315nm	R_t -6.4 min. Accuracy – 96.8% Linearity- 10-30 ppm	Nataraj K et al[14]
5	Hypersil BDS C-18 column (150 mm x 4.6 mm; 5µm)	Phosphate Buffer: Acetonitrile 85:15 v/v	1.1 ml/min. 300nm 6 min.	R_t - 3.164 min. Accuracy-99.93%. LOD- 0.23µg/ml. LOQ- 0.72µg/ml Linearity- (25-150µg/ml)	Sreedevi A et al[15]
6	Inertsil C-8 column (100 mm x 4.6 mm; 5µm)	sodium phosphate buffer, pH 6.5±0.1: methanol (70:30 v/v)	1.0 ml/min. UV at 323nm 15 min.	R_t -5.789±0.1 min. Accuracy – 99.17%. LOD- 0.448 µg/ml. LOQ- 1.348 µg/ml Linearity- (5-30 µg/ml)	Bandi R et al[16]
7	C18 RP (LiChroCART 250-4 LiChrospher 100 RP 18, 5µ, VWR)	Solvent A (40%) [water (72.5%), methanol, (25%), and triethylamine (2.5%)] : 20% Methanol :40% acetonitrile.	0.9 ml/min. UV at 267nm 10 min.	R_t -5.4(Imatinib) 3.8(Dasatinib) 7.9(Nilotinib) Accuracy - 76.41(Imatinib) 40.24(Dasatinib) 81.81(Nilotinib) LOD10ng/mL(Imatinib) 10ng/ml(Dasatinib) 50 ng/ml(Nilotinib) LOQ- 50 ng/ml(Imatinib) 50 ng/ml(Dasatinib) 100ng/ml (Nilotinib) Linearity- (0.005-10 µg/ml)	Elisa Pet al[17]
8	ThermosilC18 column (125 mm× 4.0 mm; 5µm)	Methanol: Sodium acetate buffer pH 3 (70:30 v/v)	1.0 ml/min. 252nm	R_t -2.566 min (dasatinib) 3.417 min (levatinib) Accuracy -99.56% (dasatinib) 99.48% (levatinib) LOD-3.17 (dasatinib) 5.68(levatinib) LOQ-0.0172(dasatinib) 0.2125(levatinib)	Nageswara Rao K et al[18]
9	Kromasil C18 (250 mm X 4.6 mm; 5.0 µm)	methanol:20 mM ammonium acetate pH 3.0 with acetic acid (45:55, v/v)	1ml/min. UV at 280nm	R_t - 8.23 ± 0.02 min. Linearity- (10-100 µg/ml)	Mhaske DV et al[10]

High Performance Liquid Chromatography (bio analytical)

Kassema MG et al. developed a HPLC method for determination of Dasatinib in rabbit plasma sample and applied to the determination of Dasatinib in several pharmacokinetic studies. The method achieved good resolution in short run time.[19]

Table 5: Reported HPLC (bio analytical) methods for determination of Dasatinib.

S. No	Stationary phase	Mobile phase	Flow rate and method of detection, Run time	Results	References
1	Inertsil ODS-3 (260 mm × 2.4 mm; 5µm)	0.02 M potassium dihydrogen phosphate:methanol (10:90, v/v)	2ml/min. 340nm (emission) 374 (excitation) 15 min.	R_t _1.8 min. LOD-15.0ng/ml LOQ-50.0ng/ml Linearity- (50-3000 ng/ml)	Kassema MG et al[19]

Liquid Chromatography-Mass Spectroscopy (LC-MS)

The method developed by Lakka NS et al had forced degradation under various stress condition such as hydrolytic, oxidative, thermal and photolytic stress conditions. A new degradation product obtained from acid and alkali hydrolytic conditions were identified.[21]

The advantages of developed method by Andriamanana I et al higher number of analytes in a shorter run time. It reduces the number of analysis batches and improve the efficiency. Acetonitrile has been choosen because it provide better chromatogaphic seperation than methanol. This method is enough for therapeutic requirements and PK studies.[22]

De Francia S et al developed method has good reproducibility by using small volumes of plasma(250 µl). intra- day and inter-day pecision indicates good performances of method.[27]

Thappali SRS et al developed method shows chromatographic conditions were optimized for a 5 min run time. This method involves simple LLE procedure with good sensitivity. This method involves only 50 µl blood plasma so achieved a high level of extraction efficiency.[23]

Table 6: Reported LC-MS methods for determination of Dasatinib.

S. No.	Internal Standard	Sample preparation, Stationery phase Mobile phase	Flow rate, Detection (m/z) LLOQ, Linearity	References
1	Carbamazepine	Protein precipitation sb-c18 (150 mm × 2.1 mm; 5 µm) methanol:0.1% formic acid (gradient)	0.4 ml/min. SIM-338.7 10 ng/ml Linearity- (10-1000 ng/ml)	Wen C et al[20]
2	-	C-18 Inertsil ODS-3 V, (250 mm × 4.6 mm; 5 µm) A,50 mM ammonium acetate and acetonitrile (90:10, v/v) : B acetonitrile and ultrapure water (90:10, v/v)	1.0 ml/min. 9.999 ng/ml Linearity- (0.2-3 µg/ml)	Lakka NS et al[21]
3	D8-imatinib	Gold® PFP (100 mm× 2.1 mm; 1.9 µm) A,10 mM formate ammonium buffer containing 0.1% (v/v) formic acid : B, acetonitrile with 0.1% (v/v) formic acid : C, isopropanol and acetonitrile 50:50 (v/v)	0.3 ml/min. 10ng/ml (Bortezomib, Dasatinib, Sunitinib) 150 ng/ml (Imatinib, Nilotinib, Erlotinib, Lapatinib, Sorafenib, Vandetanib) Linearity- (2-250 ng/ml)	Andriamanana I et al[22]
4	Tolbutamide	Liquid-liquid extraction C-18 column (50 mm × 3 mm; 4.6 µ) (YMC-PACK, Japan) A,methanol: B,water (gradient)	1ml/min. 455.0 > 175.0 (Methotrexate) 488.1 > 401.0 (Dasatinib) 1.0 ng/ml Linearity- (1-1000ng/ml)	Thappali SRS et al[23]
5	Dasatinib-2H8, Erlotinib-13C6, Nilotinib-2H3, Sunitinib-2H10 Gefitinib-2H8 Imatinib13C,2H3	Protein precipitation Gemini C-18 column (50 mm × 2.0 mm; 5.0 mm A,10mM ammonium hydroxide in water at pH 10.5 : B, 1mM ammonium hydroxide in	0.25ml/min. 488→401(Dasatinib) 394→278 (Erlotinib) 447→128 (Gefitinib) 494→394 (Imatinib) 581→365 (Lapatinib)	Lankheet NAG et al[24]

	Lapatinib13C,2H7 Sorafenib13C,2H3	methanol (gradient)	530→289 (Nilotinib) 465→252 (Sorafenib) 399→326(Sunitinib) Linearity- (20-10000 ng/ml)Erlotinib, Gefitinib, Imatinib, Nilotinib, Sorafenib, (5-2500 ng/ml) Dasatinib, Sunitinib.	
6	[2H8]-Ponatinib [2H9]-Bosutinib [13C6]-Trametinib [2H5]-Ibrutinib [2H8]-Dasatinib [13C6]-Cobimetinib [2H10]-Sunitinib [2H9]-Dabrafenib [13C6]-Erlotinib [13C, 2H7]-Lapatinib [13C, 2H3]-Sorafenib [2H8]-Imatinib [13C, 2H3]-Nilotinib [13C6]-Vemurafenib	Acquity UPLC BEH C-18 (50 mm × 1.9 mm × 2.1 µm) A, 10 mmol/L formate ammonium buffer containing 0.1% (v/v) formic acid : B, acetonitrile with 0.1% (v/v) formic acid (gradient)	300 ml/min. 0.75 ng/ml(Bosutinib, Ibrutinib, Trametinib,Dasatinib, and Cobimetinib) 2.5 ng/ml (Ponatinib and Sunitinib) 7.5 ng/ml (Dabrafenib, Erlotinib, Lapatinib, Sorafenib, Imatinib, Nilotinib) 250 ng/ml (Vemurafenib) Linearity – (1-500 ng/ml) Bosutinib, Cobimetinib, Dasatinib, Ibrutinib, Trametinib. (5-500 ng/ml) Ponatinib, Sunitinib.	Huynh H et al[25]
7	Quinoxaline	Atlantis T3 C-18 column (150 mm × 2.1 mm; 3.0 µm) A, water containing 0.05% formic acid, : B, acetonitrile containing 0.05% formic acid	0.25 ml/min. SIR- 493.8 (Imatinib) 487.5 (Dasatinib) 529.5 (Nilotinib) Linearity – (0.25- 50 ng/ml)	D'Avolio A et al[26]
8	Quinoxaline	Protein precipitation Atlantis T3 C18 column (150mm × 4.6mm; 5 µm) A, HPLC grade water + 0.05% formic acid : B HPLC grade acetonitrile and 0.05% formic acid	1.0 ml/min. SIR-493.8 (Imatinib) 487.5 (Dasatinib) 529.5 (Nilotinib) 78.1 ng/ml (Matinib) 62.5 ng/ml (Dasatinib and Nilotinib)	De Francia S et al[27]

Ultra Performance Liquid Chromatography-Mass Spectroscopy (UPLC-MS)

The method developed by Zeng J et al shows the advantage in the aspect of economical IS, simple sample preparation and short run time, which make it capable to analyze a large number of human plasma samples.[28]

The proposed method by Maher HM et al has many advantages including LLOQ enabling the determination of very low concentration requied for terminal phase PK studies, shorter analysis time for high throughput analysis and smaller injection volume.This method applies PPT/SPE as a superior clean-up combinational sample preparation technique poviding improved sensitivity and selectivity.[29]

Yang S et al developed a UPLC-MS/MS method for the determination of pharmacokinetic interaction between Dasatinib and Posaconazole in rat plasma samples.It shows unexpected risk when Posaconazole is co-administered with Dasatinib.[30]

Table 7: Reported UPLC-MS methods for determination of Dasatinib.

S. No.	Internal Standard	Sample preparation, Stationery phase Mobile phase, Run time	Flow rate, Detection (m/z) LLOQ, Linearity	References
1	Gliquidone	Liquid-liquid extraction Xtimate Phenyl column(150 mm×2.1mm; 3 µm) A, aqueous phase: 0.15% formic acid and 0.05% ammonium acetate and B, organic phase: acetonitrile (A:B=40:60, v/v).	0.25 ml/min. MRM- 494.5→394.5(Imatinib) 488.7→401.5(Dasatinib) 530.7→289.5(Nilotinib) 2.6 ng/ml (Imatinib) 2.0 ng/ml (Dasatinib) 2.4 ng/ml (Nilotinib)	Zeng J et al[28]
2	Erlotinib	Protein precipitation	0.2 ml/min.	Maher HM et

		Aquity BEH C-18 column Waters (100 mm × 1.0 mm; 1.7 µm) acetonitrile : 50% aqueous methanol, 65:35, v/v, each with 0.1% formic acid, 2 min.	MRM- 488.03 > 400.92 1 ng/ml Linearity- (1-500 ng/ml)	al[29]
3	Diazepam	Protein precipitation UPLC BEH C18, (100 mm × 100 mm; 1.7 µm; Waters, USA) 0.1% aqueous formic acid :acetonitrile (gradient)	0.3ml/min. MRM-488.2→401.1(Dasatinib) 701.3→683.4(Posaconozole) 1 ng/ml(Dasatinib) 5 ng/ml (Posaconozole) Linearity- (1-1000 ng/ml) dasatinib,(5-5000 ng/ml)Posaconozole	Yang S et al[30]
4	Four isotopic internal standards	Magnetic solid phase extraction Agilent Eclipse XDB-C18 column (50.0 mm × 2.1 mm; 1.7 µm) 0.1% formic acid :acetonitrile	Accuracy - 91.3–103%(Aletinib, Afatinib, Apatinib, Icotinib, Dasatinib, Crizotinib, Regorafenib, Vemurafenib, N-desmethyl imatinib) 93.8–102% (Erlotinib, Ceritinib, Imatinib, Sorafenib,Gefitinib,and Lapatinib)	Li G, Zhao M Zhao L[31]
5	2 µM testosterone in acetonitrile	Acquity UHPLC BEH C18 column (50 mm × 2.1 mm; 1.7 µm) acetonitrile/0.1% formic acid in water (gradient) 6.5 min	0.45 ml/min. SRM 3.13 nM (Erlotinib) 6.25 nM (Sunitinib, Pazopanib, and Axitinib) 12.5 nM Sorafenib, Dasatinib,Lapatinib, Nilotinib)	Yu H et al[32]
6	[$^2H_8$]-Imatinib [$^2H_{10}$]-Sunitinib	ACQUITY UPLC® BEH C_{18} column (50 mm×2.1 mm; 1.7 µm) A, acetonitrile : B, water-formic acid-ammonium acetate (1 M) (994:1:5, v/v/v)	0.4 mL/min.	Zhang M et al[33]

Ultra performance liquid chromatography, capillary zone electrophoresis, sequential injection analysis

The method developed by Garcia GA et al shows intraday, interday precision of the optimized UHPLC method was excellent and ranged from 0.18 to 1.32%. The CZE and SIA methods had a precision of up to 4.76 and 5.53%, respectively. The CZE method provides the cheapest analysis whereas the UHPLC analysis is most costly because of the high consumption of expensive organic solvents.[34]

Table 8: Reported UPLC,CZE,SIA methods for determination of Dasatinib.

S. No	Stationary phase	Mobile phase	Flow rate and method of detection	Results	References
UPLC	Acquity UPLC BEH C18 (100 mm × 2.1 mm; 1.7 µm)	Methanol: 0.1% formic acid (75:25 v/v)	0.3ml/min. 322nm	Run time- 2.0 min. Accuracy- 97.3–101.1% LOD- 0.006µg/ml LOQ-0.019µg/ml Linearity- (0.5-50 µg/ml)	Garcia GA et al[34]
CZE	Agilent 3DCE System 7100	Citrate buffer at pH 3.1 (25 mmol/l),	UV at 322nm	Run time- 2.2min. Accuracy- 95.8–100.6% LOD-0.831µg/ml LOQ-2.517 µg/ml Linearity- (5-100 µg/ml)	
SIA	FIAlab 3500 system	1.0 mol/l NaOH	745nm	Run time-2.5 min. Accuracy- 101.4–106.6% LOD-2.7 µg/ml LOQ-8.9 µg/ml Linearity – (10-100 µg/ml)	

CONCLUSION

Dasatinib is usually utilized as relapse treatment in the intense period of CML, Philadelphia chromosome-positive intense lymphoblastic leukemia. Hence worth, it is vital to developing a detailed review of different analytical methods utilized for the estimation of Dasatinib to detect the current strategies and find the necessities to future woks. The present review discussed about different analytical methods including UV Spectroscopy, HPTLC, HPLC, LC-MS, CZE, used for estimation of dasatinib from bulk pharmaceutical formulations and biological fluids. There is no UHPLC analytical method were reported. Liquid chromatography with PDA detection has been found only one method studied for estimation of Dasatinib. Few chromatography like stability- indicating LC, HPTLC are also studied. Only one CZE, SLA analysis are discussed. These completed study data used for further research in estimation of Dasatinib.

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