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METHOD DEVELOPMENT AND VALIDATION FOR ESTIMATION OF CLASS II SLOVENTS IN DASATINIB BY HSGC-FID

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ABSTRACT

A simple and selective HS-GC method is described for the determination & quantification of Residual solvents in Dasatanib API. Chromatographic separation was achieved on aDB-624 column, (50mx0.22mm) 1.8µmusing different temperature gradient of FID Detectors. Linearity was observed in the range 50-150 µg /ml for Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamide and n-hexane (r^2>0.999) forsolvent estimated in by the proposed methods was in good agreement. These methods were validated. Recovery experiments indicated the absence of interference from commonly encountered diluent and API. This method is precise as indicated by the repeatability analysis, showing %RSD less than 10 for Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamide and n-hexane. All statistical data proves validity of the methods and can be used for routine analysis of pharmaceutical active ingradients to Estimation of Residual solvents of Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamide and n-hexane in Dasatanib.

KEYWORDS: Dasatinib, HS-GC, FID Detectors, Residual solvents.

1. INTRODUCTION

Quality investigation plays a very important role in quality specification establishment of chemical drugs. The number of drugs introduced into the market every year .very often there is a time lag from the date of introduction of a drug into the market to the date of its inclusion in pharmacopoeias. Hence, standards and analytical procedures for these drugs may not be available in the pharmacopoeias. It becomes necessary, therefore to develop newer analytical methods for such drugs. Solvents used in the manufacture of active pharmaceutical ingredients (APIs) or drug substances and excipients or in the formulation of drug products are often necessary.

Literature survey reveals that no analytical method was reported earlier for estimation of residual solvents in Dasatinib by HS-GC. The main aim is to develop an accurate, precise, sensitive, selective, reproducible and rapid analytical technique for estimation of class II solvents in Dasatinib.

Table 1: Literature Review.

Author	Title
ZhenLiu, HuajunFan, YihuiZhou, Xiaowei Qian, JihuiTu, BinChen et al.,[15]	Development and Validation of a sensitive method for alkyl sulphonate genotoxic impurities determination in drug substances using Gas Chromatography coupled to triple quadrupole mass spectrometry.
M. Rajavardhan Reddy* and R. Suresh et al.,[9]	Chemometrics assisted RP-HPLC method development for the separation of second generation Tyrosine Kinase Inhibitors in bulk drugs and pharmaceutical formulations.

Solubility determination of Dasatanib by various Residual solvents. Determine the Physical properties like Boiling point, Solubility, Polarity etc Optimize the Gas chromatography conditions for proper resolution and retention times. Validate the developed method as per ICH guidelines.

Dasatinib, sold under the brand name Sprycel, is a targeted therapy used to treat certain cases of chronic myelogenous leukemia (CML) and acute lymphoblastic leukemia (ALL).Specifically it is used to treat cases that are Philadelphia chromosome-positive. It is taken by mouth.

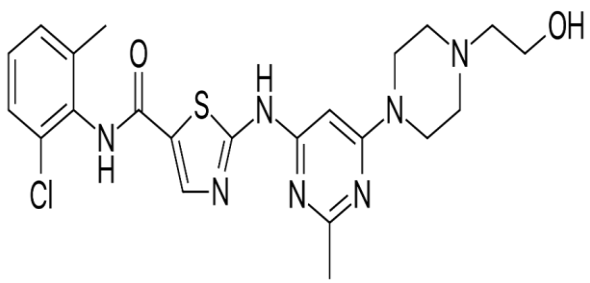

Fig 1: Chemical structure of Dasatanib.

- **IUPAC Name:** N-(2-chloro-6-methylphenyl)-2-[[6-[4-(2-hydroxyethyl)-1-piperazinyl]-2-methyl-4-pyrimidinyl]amino]-5-thiazole carboxamide monohydrate

MolecularFormula: $C_{22}H_{26}ClN_7O_2S$
Molecular Weight: 488.01 g/mol $g \cdot mol^{-1}$
Category: Antineoplastic agent

Mechanism of Action
Dasatinib, at nanomolar concentrations, inhibits the following kinases: BCR-ABL, SRC family (SRC, LCK, YES, FYN), c-KIT, EPHA2, and PDGFRβ. Based on modeling studies, dasatinib is predicted to bind to multiple conformations of the ABL kinase. In vitro, dasatinib was active in leukemic cell lines representing variants of imatinib mesylate sensitive and resistant disease. Dasatinib inhibited the growth of chronic myeloid leukemia (CML) and acute lymphoblastic leukemia (ALL) cell lines overexpressing BCR-ABL. Under the conditions of the assays, dasatinib was able to overcome imatinib resistance resulting from BCR-ABL kinase domain mutations, activation of alternate signaling pathways involving the SRC family kinases (LYN, HCK), and multi-drug resistance gene overexpression.

Indication
For the treatment of adults with chronic, accelerated, or myeloid or lymphoid blast phase chronic myeloid leukemia with resistance or intolerance to prior therapy. Also indicated for the treatment of adults with Philadelphia chromosome-positive acute lymphoblastic leukemia with resistance or intolerance to prior therapy.

3. MATERIALS AND METHODS

Drug used: Dasatinib API

Table 3.1: Instruments used.

Gas Chromatography Make	Agilent Infinity
Gas Chromatography Model	7697A
Software for Data Acquisiton	Open labs EZchrome
Electronic balance	Metler Toledo
Gas Chromatography Column	DB-624 column, (50mx0.22mm) 1.8µm

Table 3.2: Reagents used

Dimethyl Sulfoxide	GC Grade(Make: Qualigens)
Methanol	GC Grade(Make: Qualigens)
Toluene	GC Grade(Make: Sigma Aldrech)
Actonitrile	GC Grade(Make: Sigma Aldrech)
Methylene chloride	GC Grade(Make: Sigma Aldrech)
Dimethyl formamide	GC Grade(Make: Sigma Aldrech)
N-hexane	GC Grade(Make: Qualigens)

4. SELECTION AND DESCRIPTION OF PARTICIPANTS

4.1 Solubility Studies for active entity

These studies are carried out at 25^0C
The solubility of Dasatanib(active entity)is soluble in organic solvents such as Acetonitile, Toulene, Methylene chloride, dimethyl formamide (DMF) and n-hexane. In DMSO has high solubility, so DMSO is used as diluent.
Solvents to be quantified
1.0 Acetonitile
2.0 Toulene
3.0 Methylene chloride
4.0 Dimethyl formamide
5.0 N-hexane

4.2 Determination of Boiling Points

Table 4.1: Boiling points.

S.No	Solvents Name	Temperature(°C)
01	Acetonitile	82.1
02	Toulene	110.6
03	Methylene chloride	39.6
04	Dimethyl formamide	34.6
05	N-hexane	68.0

Preparation of Diluent: Use Dimethyl sulfoxide (DMSO)

Preparation of Blank
Transfer 1.0 ml of diluent in headspace vial and seal the vial immediately.

Standard Sock-I Preparation
Weigh accurately about 500 mg of Acetonitrile, 500 mg of Toulene, 500 mg of Methylene Chloride, 500mg of Dimethyl formamide and 500 mg of n-hexane in 250ml Volumetric flask containing about 180 ml of diluent, make up to volume with diluent and shake well.

Standard Sock-II Preparation
Pipette out 10 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.
Pipette 1 ml of above prepared solution in headspace vial &seal the vial.

Test Sample Preparation
Weigh accurately about 500 mg of test sample (DasatanibAPI) and transfer in to 50mL volumetric flask add 35mL of Diluent, vortex it for 5min. Then make up the volume with diluent and mix well.

Pipette 1 ml of above prepared solution in headspace vial andseal the vial.

4.3 METHOD DEVELOPMENT OF RESIDUAL SOLVENTS
GC Parameter and Condition
Column:DB-624 column, (50mx0.22mm) 1.8µm
Inlet Temperature: 150°C
Detector Temperature: 220°C
Initial Oven Temperature: 50°C
FinalOven Temperature: 150°C
Carrier Gas: Nitrogen
Flow: 4.0 ml/min.
Split Ratio: 2 :10

Head Space Conditions
Oven Temp. : 80°C
Transfer line Temp. : 90°C
GC cycle Time : 20 min.
Loop Fill Temperature : 100 °C

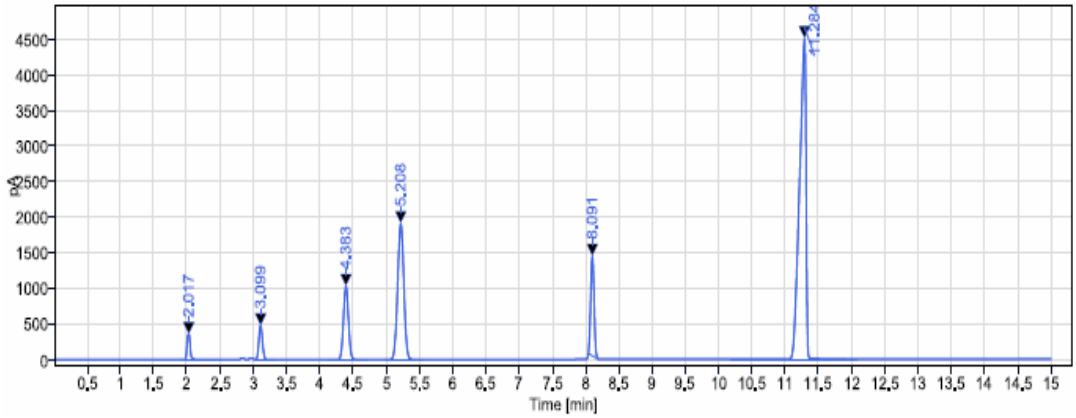

Fig 1: Chromatogram of optimized trail.

OBSERVATION
All Solvent Peaks were separated with good resolution and good efficiency, this Trial taken as a Optimised Trial.

5. TECHNICAL INFORMATION
5.1 System Suitability and System Precision
Preparation of Diluent: Use Dimethyl sulfoxide (DMSO)

Standard Sock-I Preparation
Weigh accurately about 500 mg of Acetonitrile, 500 mg of Toulene, 500 mg of Methylene Chloride, 500mg of Dimethyl formamide and 500 mg of n-hexane in 250ml Volumetric flask containing about 180 ml of diluent, make up to volume with diluent and shake well.

Standard Sock-II Preparation
Pipette out 10 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.
Pipette 1 ml of above prepared solution in headspace vial &seal the vial.

5.2 Specificity by Direct comparison method
There is no interference of Diluent with the solvent peak and no interference of the API peak at the retention time of the solvent peaks.

Preparation of Diluent: Use Dimethyl sulfoxide (DMSO)

Preparation of Blank
Transfer 1.0 ml of diluent in headspace vial and seal the vial immediately.

Standard Sock-I Preparation
Weigh accurately about 500 mg of Acetonitrile, 500 mg of Toulene, 500 mg of Methylene Chloride, 500mg of Dimethyl formamideand 500 mg of n-hexanein 250ml Volumetric flask containing about 180 ml of diluent, make up to volume with diluent and shake well.

Standard Sock-II Preparation
Pipette out 10 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.

Pipette 1 ml of above prepared solution in headspace vial &seal the vial.

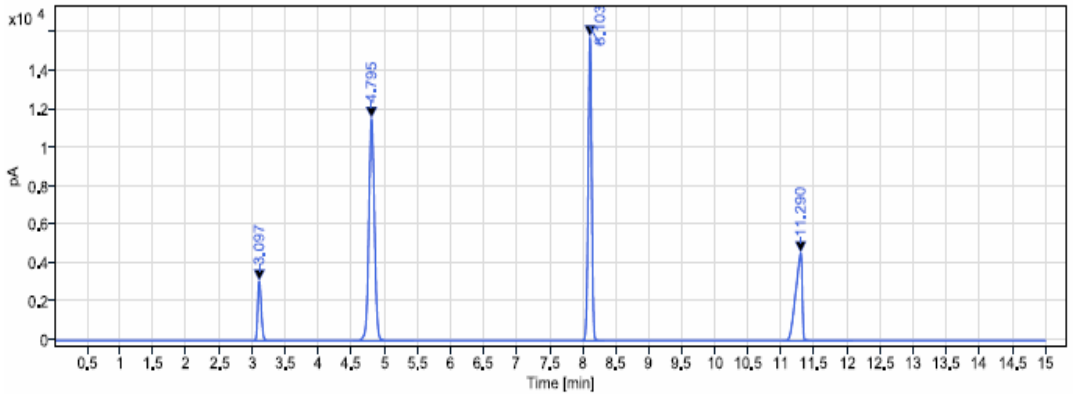

Fig5.2.1: Blank chromatogram for specificity.

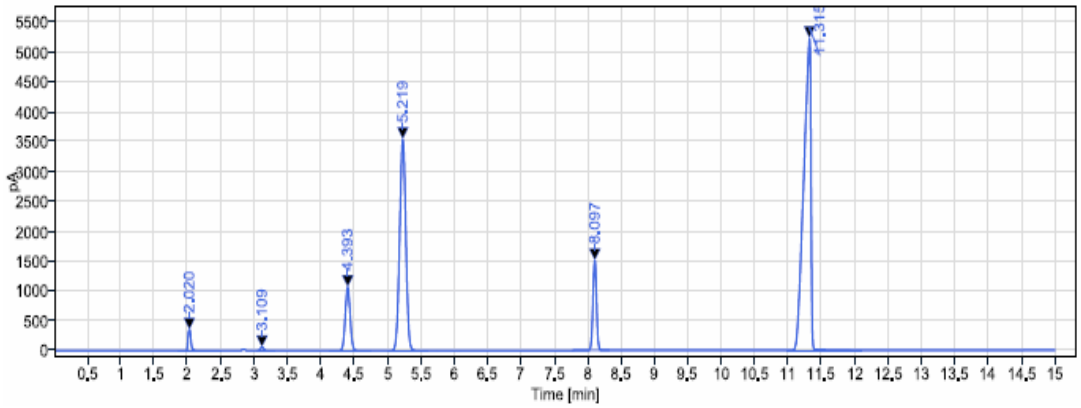

Fig. 5.2.2: Chromatogram for specificity of standard.

Observation

It is observed from the above data, diluent or API peaks are not interfering with the Solvent peaks i.e., Acetonitrile, Toulene,Methylene Chloride, Dimethyl formamide, n-hexane.

5.3 Linearity and range

Standard Sock-I Preparation

Weigh accurately about 200 mg of Acetonitrile, 200 mg of Toulene, 200 mg of Methylene Chloride,200mg ofDimethyl formamideand 200 mg of n-hexanein 100ml Volumetric flask containing about 20 ml of diluent, make up to volume with diluent and shake well.

Table 5.3.1: Linearity Preparations.

Preparations	Volume from standard stock transferred in ml	Volume made up in ml (with mobile phase)	Concentration of solution(µg /ml) Acetonitrile, DMFMethylene Chloride, Toulene and n-hexane
Preparation 1	2.5	100	50
Preparation 2	3.75	100	75
Preparation 3	5	100	100
Preparation 4	6	100	120
Preparation 5	7.5	100	150

5.4 Accuracy

Accuracy of the method was determined by Recovery studies. To the API (pre analyzed sample), the SOLVENTS were added at the level of 50%, 100%, 150%. The recovery studies were carried out three times and the percentage recovery and percentage mean recovery were calculated for drug is shown in table. To check the accuracy of the method, recovery studies were carried out by addition of standard drug solution to pre-analyzed sample solution at three different levels 50%, 100% & 150%.

Standard Sock-I Preparation

Weigh accurately about 500 mg of Acetonitrile, 500 mg of Toulene, 500 mg of Methylene Chloride, 500mg ofDimethyl formamideand 500 mg of n-hexanein 250ml Volumetric flask containing about 180 ml of diluent, make up to volume with diluent and shake well.

Standard Sock-II Preparation for 50% Accuracy
Pipette out 5 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.

Standard Sock-II Preparation for 100% Accuracy
Pipette out 10 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.

Standard Sock-II Preparation for 150% Accuracy
Pipette out 7.5 ml of above solution in 100 ml volumetric flask containing about 20 ml diluent, make up to volume with diluent.

Test Sample Preparation for 50% Accuracy
Weigh accurately about 500 mg of test sample (Dasatanib API) and transfer in to 25mL volumetric flask add 15mL of standard stock-II, vortex it for 5min. Then make up the volume with standard stock-II for 50% Accuracy and mix well.
Pipette 1 ml of above prepared solution in headspace vial andseal the vial.
***Above preparations were prepared three times and injected through head space

Test Sample Preparation for 100% Accuracy
Weigh accurately about 500 mg of test sample (Dasatanib API) and transfer in to 25mL volumetric flask add 15mL of standard stock-II, vortex it for 5min. Then make up the volume with standard stock-II for 100% Accuracy and mix well.
Pipette 1 ml of above prepared solution in headspace vial andseal the vial.
***Above preparations were prepared three times and injected through head space

Test Sample Preparation for 150% Accuracy
Weigh accurately about 500 mg of test sample (Dasatanib API) and transfer in to 25mL volumetric flask add 15mL of standard stock-II, vortex it for 5min. Then make up the volume with standard stock-II for 150% Accuracy and mix well.
Pipette 1 ml of above prepared solution in headspace vial andseal the vial.
***Above preparations were prepared three times and injected through head space.

5.5 Precision
Method precision
Standard Sock-I Preparation
Weigh accurately about 500 mg ofAcetonitrile, 500 mg of Toulene, 500 mg of Dichloromethane 500mg of Methylene Chloride and n-hexane in250ml Volumetric flask containing about20 ml of diluent, make up to volume with diluent and shake well.

Standard Sock-II Preparation
Pipette out 10 ml of above solution in 200 ml volumetric flask containing about 20 ml diluent, make up to volume with diluents.

Method Precision Sample-I
Weigh accurately about 500 mg of test sample (Dasatanib API) and transfer in to 25mL volumetric flask add 18mL of standard stock-II, vortex it for 5min. Then make up the volume with standard stock-II and mix well.
Pipette 1 ml of above prepared solution in headspace vial andseal the vial.
***Above preparations were prepared six times and injected through head space

5.6 Limit of Detection.

$$LOD = \frac{3.3\sigma}{S}$$

Where, σ = the standard deviation of the response
S = the slope of the calibration curve
The slope S may be estimated from the calibration curve of the analyte.

5.7Limit of Quantification

$$LOQ = \frac{10\sigma}{S}$$

Where, σ = the standard deviation of the response
S = the slope of the calibration curve
The slope S may be estimated from the calibration curve of the analyte.

6. RESULTS
Table 6.1: System suitability of solvents.

Sovent Name	**Acetonitrile**		**Toulene**		**Methylene Chloride**		**Dimethyl Formamide**	
S.No	Rt	Area	Rt	Area	Rt	Area	Rt	Area
1	2.019	1042.24	3.107	1745.38	4.381	5104.25	5.211	12732.28
2	2.017	1064.24	3.099	1727.46	4.381	5193.78	5.215	12425.34
3	2.016	1061.19	3.105	1741.39	4.387	5125.24	5.198	12593.63
4	2.020	1037.46	3.104	1746.68	4.218	5087.51	5.187	12834.84
5	2.021	1052.48	3.106	1726.76	4.391	5078.26	5.232	12671.39
6	2.017	1021.34	3.101	1748.47	4.389	5054.28	5.239	12417.53
Avg	2.0183	1046.492	3.104	1739.357	4.3578	5107.220	5.2137	12612.502
St.dev	0.0020	16.119	0.003	9.770	0.0686	48.695	0.0197	167.719
%RSD	**0.10**	**1.54**	**0.10**	**0.56**	**1.57**	**0.95**	**0.38**	**1.33**

n-hexane	
Rt	Area
8.097	4938.45
8.091	4967.58
8.095	5039.25
8.094	5038.64
8.093	5125.19
8.092	4986.37
8.0937	5015.91
0.0022	66.65
0.03	**1.33**

Acceptance Criteria: %RSD of responses of each solvents should be NMT 10%

Observation

%RSD of responses of each solvents were found to be less than 10%

Table 6.2: Linearity of Acetonitrile.

S.No.	Conc.(µg/ml)	Area
1	50	451.96
2	75	856.09
3	100	1225.23
4	120	1540.95
5	150	1955.78

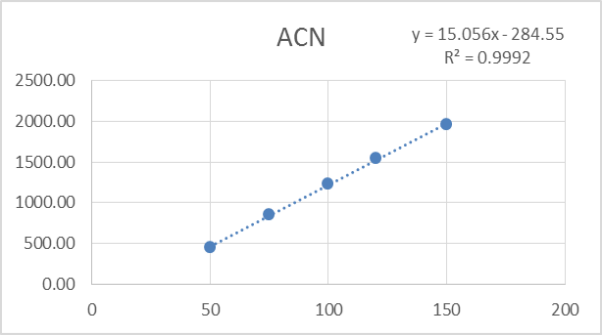

Fig 6.1 Linearity graph of Acetonitrile.

Table 6.3: linearity of Dimethyl Formamide.

S.No.	Conc.(µg/ml)	Area
1	50	4098.43
2	75	12415.81
3	100	21191.11
4	120	28306.73
5	150	37371.90

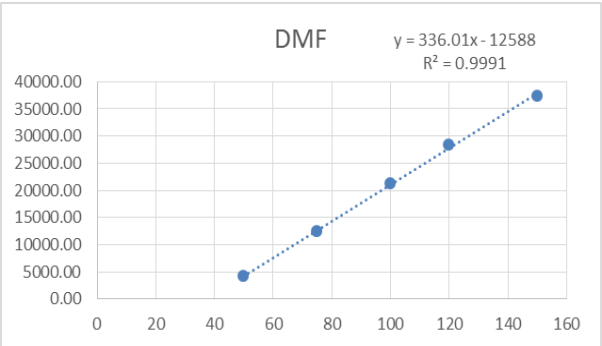

Fig 6.2: Linearity graph of Dimethyl Formamide.

Table 6.4: linearity of Toulene.

S.No.	Conc.(µg/ml)	Area
1	25	432.82
2	50	872.19
3	75	1288.18
4	100	1745.23
5	150	2616.97

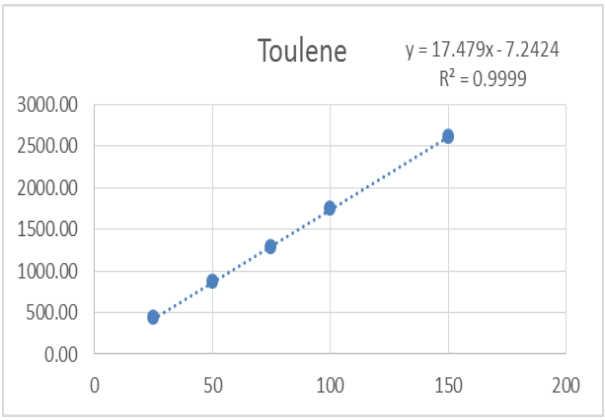

Fig. 6.3: Linearity graph of Toulene.

Table 6.5: linearity of Methylene Chloride.

S.No.	Conc.(µg/ml)	Area
1	25	1669.66
2	50	3299.89
3	75	4716.82
4	100	6450.47
5	150	9517.03

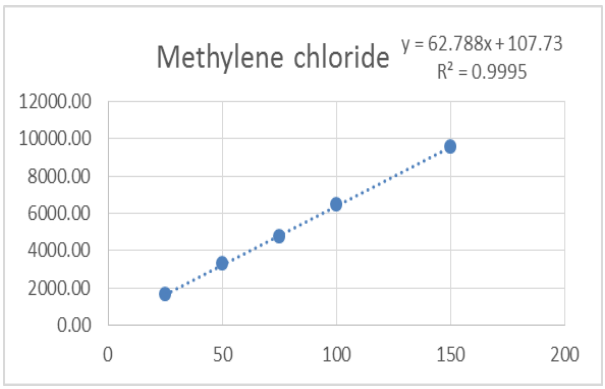

Fig 6.4: Linearity graph of Methylene Chloride.

Table 6.6: Linearityof n-hexane.

S.No.	Conc.(µg/ml)	Area
1	50	1695.35
2	75	3883.83
3	100	5923.95
4	120	7465.45
5	150	9822.81

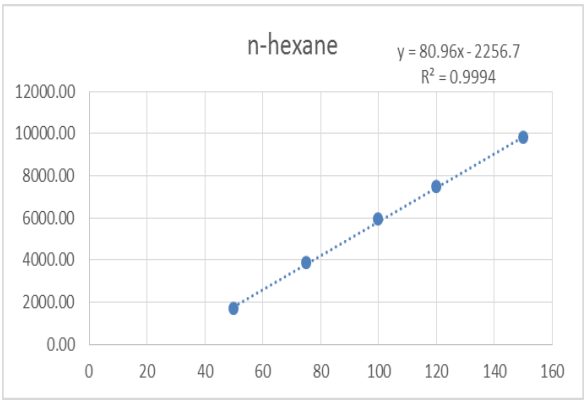

Fig. 6.5: Linearity graph of n-hexane.

Acceptance criteria

The relationship between the concentrations& responses of **Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamideand n-hexane**should be linear in the specified range and the correlation should not be less than 0.99.

Observation

The correlation coefficient for linear curve obtained between concentration vs. Area for standard preparations of **Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamideand n-hexane**is >0.999 is linear in the range examined since all points lie in a straight line and the correlation coefficient is well within limits.

Table 6.7: **Recovery Results for Solvents.**

% Level	Acetonitrile	Toulene	Methylene chloride	DMF	n-hexane
50 %	100.66	101.75	100.41	99.38	101.73
100 %	103.24	101.93	100.30	100.53	100.37
150 %	99.75	102.12	100.21	101.64	100.14

Observation

The percentage mean recovery of all solvents were obtained between 80% to 120%.

Table 6.8: Results for Method precision of solvents.

Sovent Name	Acetonitrile		Toulene		Methylene Chloride		DMF	
S.No	Rt	Area	Rt	Area	Rt	Area	Rt	Area
1	2.020	1036.03	3.103	1742.06	4.387	5104.03	5.213	12718.00
2	2.017	1074.51	3.099	1707.79	4.383	5193.99	5.208	12410.10
3	2.017	1069.30	3.099	1791.26	4.383	5093.89	5.208	12589.25
4	2.020	1039.82	3.102	1776.8	4.212	5033.61	5.212	12833.61
5	2.021	1052.53	3.104	1726.04	4.389	5089.32	5.215	12663.64
6	2.017	1023.24	3.099	1726.04	4.389	5061.44	5.208	12410.10
avg	2.0187	1049.238	3.101	1744.998	4.3572	5096.047	5.2107	12604.117
stdev	0.0019	19.955	0.002	32.445	0.0712	54.410	0.0031	170.109
%RSD	**0.09**	**1.90**	**0.07**	**1.86**	**1.63**	**1.07**	**0.06**	**1.35**

n-hexane	
Rt	Area
8.093	4940.43
8.091	4973.46
8.091	5036.11
8.093	5023.67
8.094	5130.00
8.091	4973.21
8.0922	5012.81
0.0013	67.45
0.02	**1.35**

Table 6.9: LOD and LOQ of solvents.

Name of the Parameter	Acetonitrile in ppm	Toulene in ppm	Methylene chloride in ppm	DMF in ppm	n-hexanein ppm
Limit of Detection	3.53	1.84	2.55	1.64	2.71
Limit of Quantification	10.70	5.58	7.75	4.99	8.23

From the above results six LOQ Samples were prepared in above LOQ concentration by diluting the standard solution and spiked on diluent and injected in to HS-GC.

Acceptance criteria

From the above study upon changing the flow rates theoretical plate count (NLT-2000) and tailing factor (NLT 2.0) were found to be within limits.

Table 6.10: Robustness at Low Flow Rate.

Sovent Name	Robustness of low flow rate		
	Rt	TP	Tailing factor
ACN	2.026	8930	1.14
Toulene	3.112	13895	1.07
Methylene Chloride	4.400	15148	1.03
DMF	5.228	14482	1.00
n-hexane	8.106	10369	0.99

Table 6.11: Robustness at high flow rate.

Sovent Name	Robustness of high flow rate		
	Rt	TP	Tailing factor
CAN	2.028	8694	1.12
Toulene	2.838	12265	1.03
Methylene Chloride	4.401	15120	1.02
DMF	5.229	14480	0.99
n-hexane	8.105	10344	0.99

Table 6.12: Results for ruggedness.

Sovent Name	Acetonitrile		Toulene		Methylene Chloride		Dimethyl Formamide	
S.No	Rt	Area	Rt	Area	Rt	Area	Rt	Area
1	2.023	1052.32	3.109	1835.57	4.398	4957.67	5.226	13826.57
2	2.023	1024.31	3.109	1662.48	4.397	4696.52	5.225	12286.58
3	2.023	1037.66	3.109	1783.57	4.398	4828.81	5.225	13173.28
4	2.023	1019.89	3.109	1664.97	4.398	4702.80	5.226	12101.53
5	2.023	1039.95	3.109	1797.29	4.398	4857.57	5.226	13011.20
6	2.023	1035.76	3.109	1691.17	4.398	4780.68	5.226	12038.42
avg	2.0230	1034.982	3.109	1739.175	4.3978	4804.008	5.2257	12739.597
stdev	0.000	11.617	0.000	75.277	0.0004	99.435	0.0005	713.773
%RSD	**0.00**	**1.12**	**0.00**	**4.33**	**0.01**	**2.07**	**0.01**	**5.60**

n-hexane	
Rt	Area
8.105	4868.57
8.104	4664.89
8.103	4745.24
8.104	4669.56
8.105	4784.26
8.105	4747.50
8.1043	4746.67
0.0008	76.04
0.01	**1.60**

Acceptance Criteria: %RSD of responses of each solvents should be NMT 10%
Observation
%RSD of responses of each solvents were found to be less than 10%.

7. DISCUSSION.

Sno.	Parameter	Observation	Acceptance criteria
1.	System suitability %RSD	Less than 10%	Not more than 10%
2.	Specificity	No interference of diluent or API peaks with the solvents.	No interference of diluents with the solvent peak and no interference of API peak at the retention time of the solvent peaks.
3.	Linearity Slope – P1 P2 P3 P4 P5 Correlation coefficient	50-150 µg/ml 0.9992 0.9991 0.9999 0.9995 0.9994 Less than and equal to 0.9999	Should not be less than 0.9999
4.	Accuracy Mean % recovery	Between 80% to 120%	Should be between 80% to 120%
5.	Precision % RSD	2%	Not more than 15.0%
6.	Robustness Flow rate variation Tailing factor	less than or equal to 2000 less than 2.0	Not less than 2000 Not less than 2.0
7.	Ruggedness %RSD of solvents	less than 10%	Not more than 10%

8. CONCLUSION

From the above experimental results and parameters it was concluded that, this newly developed method for the estimation ofResidual solvents of Acetonitrile, Toulene, Methylene Chloride, Dimethyl formamide and n-hexane in Dasatanib API was found to be simple, precise, accurate and high resolution and shorter retention time makes this method more acceptable and cost effective and it can be effectively applied for routine analysis in research institutions, quality control department in industries, approved testing laboratories, bio-pharmaceutical and bio-equivalence studies and in clinical pharmacokinetic studies in near future.

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