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DETERMINATION AND VALIDATION FOR ACETIC ACID CONTENT PRESENT IN FLURBIPROFEN BY GC-HS TECHNIQUE

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Abstract

Most solvents are organic volatile chemicals that are used in the manufacture of APIs, excipients and pharmaceuticals. Therefore, there is no therapeutic use of such solvents and they also affect the quality and stability of not only drugs but also their product and should be eliminated to the extent possible to meet product specifications and other quality-based requirements. These residual solvents cannot be completely removed; therefore, they should be within acceptable limits according to regulatory guidelines such as ICH guidelines. GC-HS is the most commonly used technique used for the analysis of volatile solvents. The aim of this work is therefore to develop a simple, specific GC-HS method for the determination of residual solvents in Flurbiprofen. The method was developed accurately and validation parameters were explained. Chromatographic condition was RDS/AL/GC – 03 Parkin Elmer instrument and RDS/AL/GC – 05 by Agilent, column: GSBP- 624 (30m x 0.53 mm x 3.0 µm). The parameters like as Specificity, Precision, Accuracy, Linearity and Range, Limit of Detection (LOD) and Limit of Quantitation testing with Acetone, Benzene, Dichloromethane, Ethyl Acetate, Toluene, Isopropyl alcohol and Bromobenzene. All validation parameters are used in the routine and stability analysis.

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Introduction:-

Flurbiprofen is used to relieve pain, tenderness, swelling and stiffness caused by osteoarthritis (arthritis caused by the destruction of the joint lining) and rheumatoid arthritis (arthritis caused by swelling of the joint lining). Flurbiprofen belongs to a class of drugs called non-steroidal anti-inflammatory drugs (NSAIDs). This drug works by stopping the production of substances that cause pain, fever and inflammation in the body (*Townsend et al., 2005 & Cudaback et al., 2014*). Flurbiprofen is a non-steroidal anti-inflammatory agent, one of the propionic acid groups, which has significant anti-inflammatory, analgesic and antipyretic properties (*Tomonobu et al., 2014*). Clinically, it is used for the treatment of rheumatoid arthritis, degenerative joint disease, osteoarthritis, ankylosing spondylitis, acute Musculo skeletal disorders, low back pain and allied conditions (*Rousseau et al., 2008*).

Common Name	Flurbiprofen
IUPAC	2-(2-fluoro[1,1'-biphenyl]-4-yl)propanoic acid
Molecular Weight	244.25
Molecular Formula	$C_{15}H_{13}FO_2$

Material and Methods:-

Instruments

	Instrument Name	Instrument Number	Instrument Make
1	GC-HS	RDS/AL/GC - 03	Perkin - Elmer
2	GC-HS	RDS/AL/GC - 05	Agilent
3	Semi-micro balance	RDS/AL/BAL - 10	Mettler- Toledo

Columns:

	Column Number	Column Make	Dimension
1	AMD/CAP/069	GS-TEK	GSBP- 624 (30m x 0.53 mm x 3.0 µm)
2	AMD/CAP/073	GS-TEK	GSBP- 624 (30m x 0.53 mm x 3.0 µm)

Chemicals: Methanol, Acetone, Isopropyl Alcohol, dichloromethane, n-Hexane, Benzene, Toluene and Acetic acid was used by HPLC grade. Bromobenzene was used by synthesis grade. Dimethyl sulphide was used by GC-HS grade and Flurbiprofen was used EP grade provided by Supriya Life sciences.

Preparation of standard stock solution

Solvent	Wt(mg)	Dilution (ml)	Conc(ppm)	% assay
Acetic acid	253.15	50	5053.38	99.81

Preparation of standard solution

Solvent	Volume (ml)	Conc(ppm)	Dilution (ml)
Acetic acid	2.5	252.67	50

Result and Discussions:-

System suitability:

System suitability testing is an integral part of gas and liquid chromatography methods. These are used to ensure that the resolution and repeatability of the chromatographic system is sufficient to perform the analysis (*Lokhande et al., 2017*). System suitability is checking the system to confirm its performance before or during the analysis of unknowns. It was determined by performing six replicate injections of standard solution as per method of analysis and analyzed.

Table 1:- System suitability.

Inj.#	RT(min)	Area
Inj.-1	9.043	186276
Inj.-2	9.040	185287
Inj.-3	9.029	192512
Inj.-4	9.045	200757
Inj.-5	9.043	198073
Inj.-6	9.031	189100
Mean	**9.039**	**192001**
SD	**0.010**	**6325.62**
%RSD	**0.11**	**3.29**

Acceptance criteria: RSD of area of Acetic acid derivative of six standard solution injections should be NMT 10.0%.

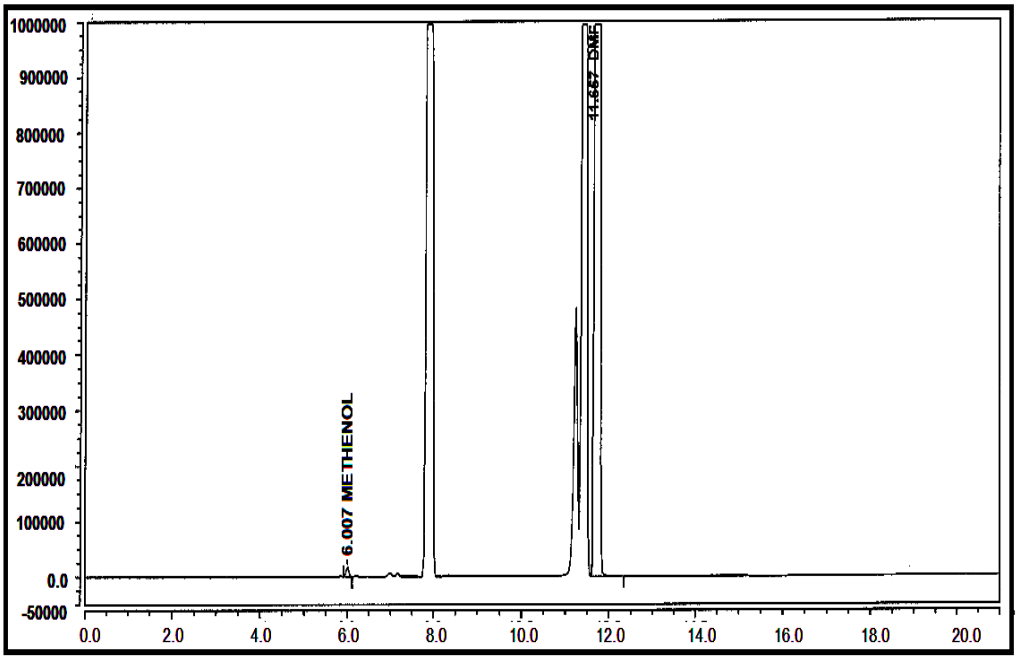

Figure 1:- Blank Methanol.

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	11.665	DMF	BMB	9975374	100	1.0	2.94	28648	NA
Total				9975374	100	1.0			

Specificity:
Specificity studies should be performed during validation of identity testing, impurity determination, and assay. The method used to represent the property depends on the purpose of the analytical method (*ICH Q2(R-1), 2005*). It is not always possible to prove that an analytical method is specific for a particular analyte (complete identification). In this case, a combination of two or more analytical steps is recommended to achieve the required level of discrimination. All solvents were prepared individually and all these solutions were analysis.

Table 2:- Specificity.

Component	RT(min)	RRT
Methenol	6.007	0.51
Ethenol	6.939	0.59
Benzene	8.233	0.70
Ethyl acetate	7.269	0.61
Acetic acid derivative	9.039	0.77
Triethyl amine	8.279	0.71
Isobutanol	9.500	0.81
Tetra chloro ethylene	10.301	0.88
Toluene	10.961	0.94
Dimethyl sulfoxide	11.657	1.00

Acceptance criteria:
Peak due to Acetic acid derivative should be adequately resolved from all other solvents and diluent.

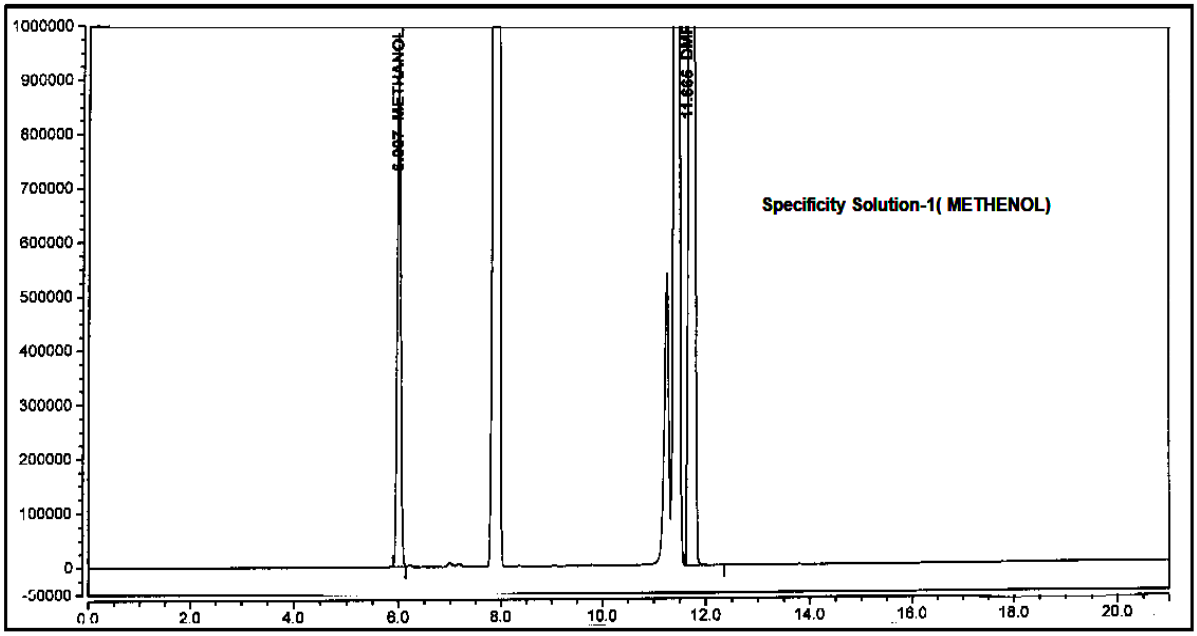

Figure 2:- Specificity solution-1 (Methanol).

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	11.665	DMF	BMB	9975374	100	1.0	2.94	28648	NA
Total				9975374	100	1.0			

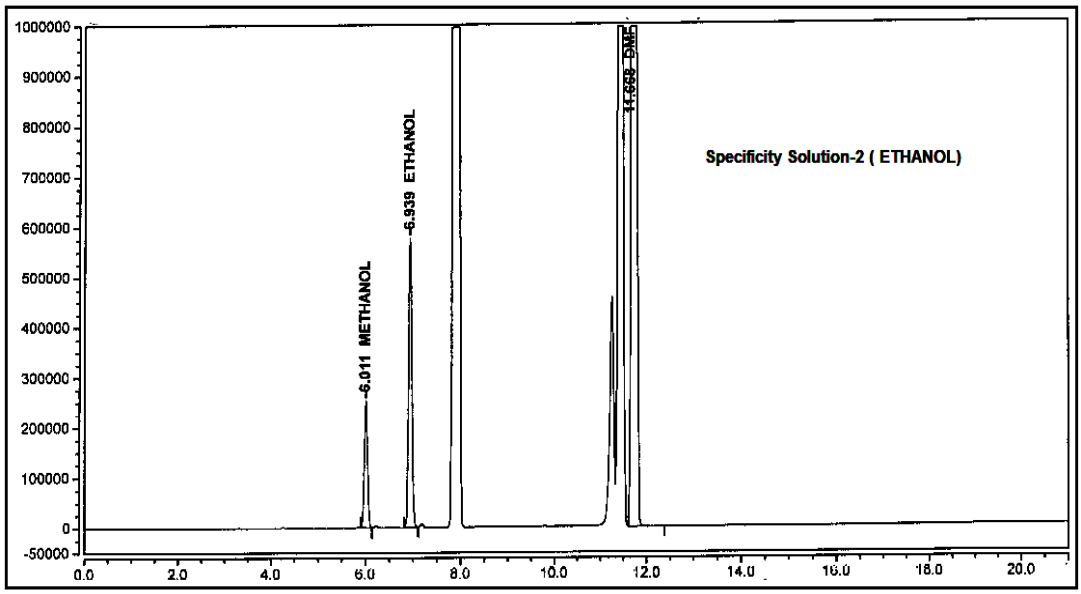

Figure 3:- Specificity solution-2 (Ethanol).

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.011	Methanol	BMB	1144659	8.25	0.51	1.03	39361	NA
2	6.939	Ethanol	BMB	2614843	18.85	0.59	1.02	53030	7.71
3	11.668	DMF	BMB	10105033	72.89	1.00	2.87	27839	23.70
Total				13864535	100.0				

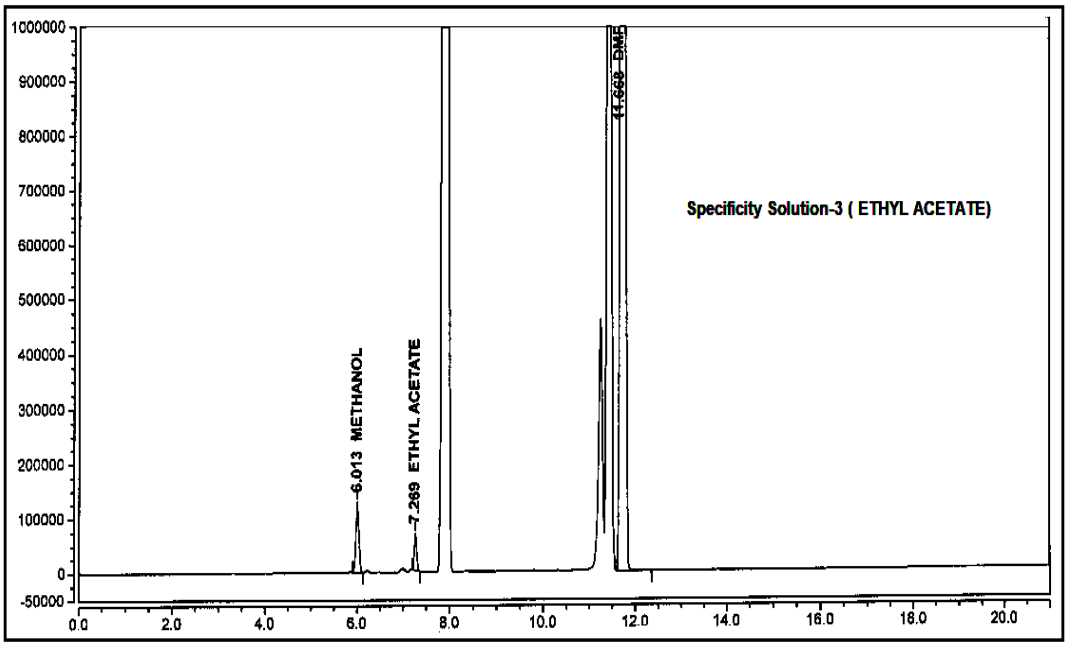

Figure 4:- Specificity solution-3(Ethyl Acetate).

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.013	Methanol	BMB	579248	5.37	0.51	1.01	40730	NA
2	7.269	Ethyl Acetate	BMB	230228	2.14	0.63	1.13	101973	11.99
3	11.668	DMF	BMB	9994231	92.49	1.00	2.84	28460	23.98
Total				10803708	100.0				

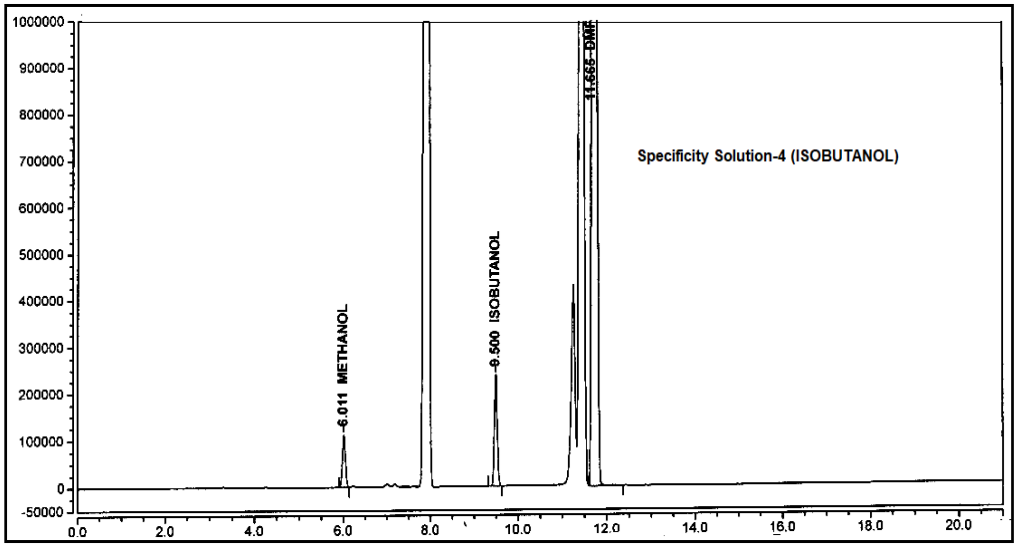

Figure 5:- Specificity solution-4 (Isobutanol).

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.011	Methanol	BMB	500117	4.31	0.51	1.02	40402	NA

2	9.500	Isobutanol	BMB	1010949	4.75	6.75	1.01	111559	29.99
3	11.665	DMF	BMB	10059210	86.95	1.00	2.90	28192	11.08
Total				11570277	100.0				

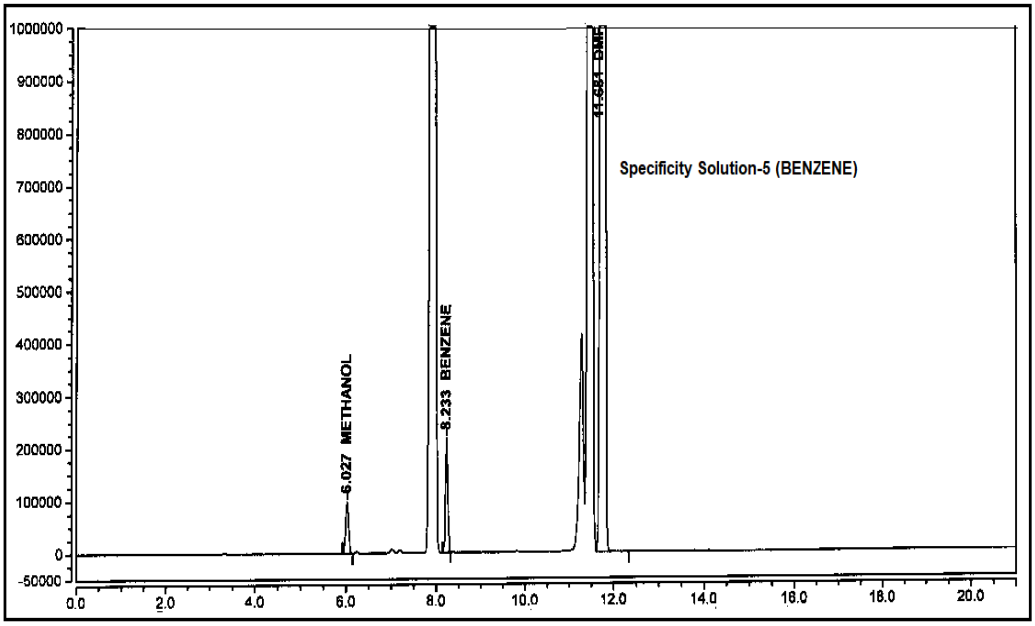

Figure 6:- Specificity solution-5 (Benzene).

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.027	Methanol	BMB	437111	3.84	0.51	1.02	40462	NA
2	8.233	Benzene	BMB	756901	6.65	0.71	1.00	126090	20.81
3	11.681	DMF	BMB	10179768	89.50	1.00	2.88	27615	18.50
Total				11373778	100.0				

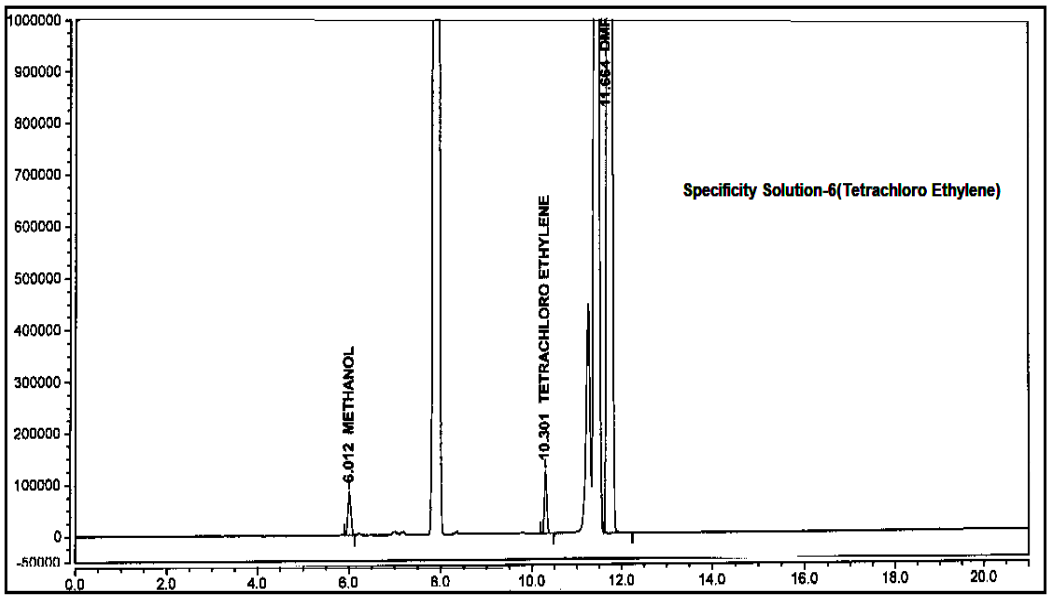

Figure 7:- Specificity solution-6, Tetra chloroethylene.

Peak	RT	Peak Name	Type	Area µV*	%	R.R.T	Asymmetry	Plates	Resolution

	(min)			sec	Area			(EP)	(EP)
1	6.027	Methanol	BMB	378431	3.43	0.52	1.01	40541	NA
2	10.301	Tetrachloride Ethylene	BMB	414035	3.75	0.88	1.01	204285	40.84
3	11.664	DMF	BMB	10213555	92.82	1.00	2.97	27351	7.33
Total				11006022	100.0				

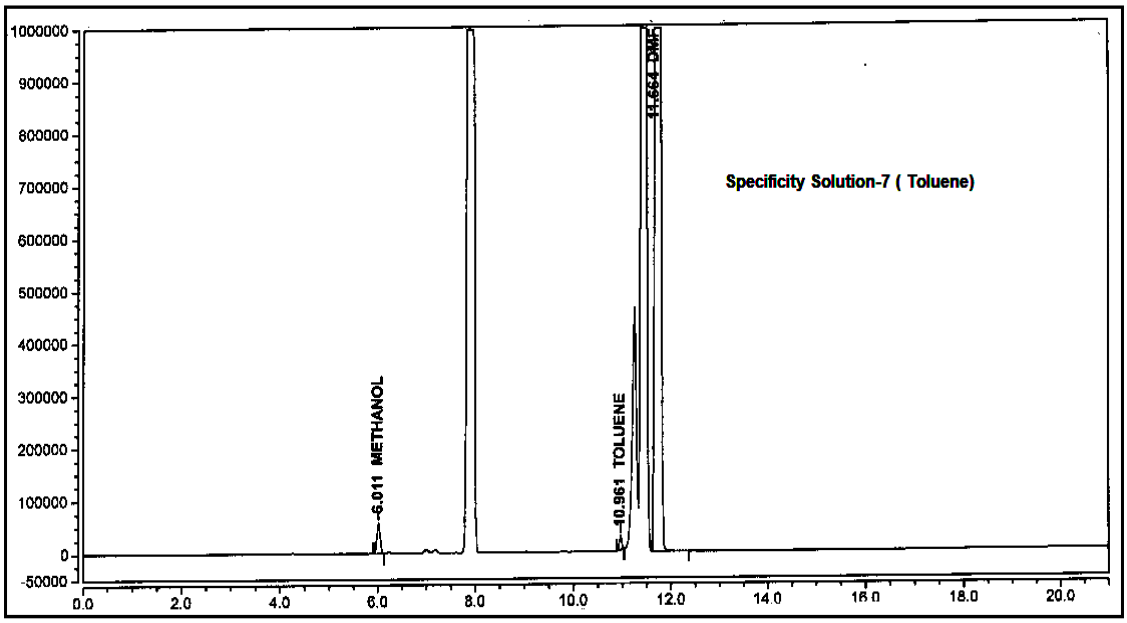

Figure 8:- Specificity solution-7, Toluene.

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.027	Methanol	BMB	262728	2.51	0.51	1.03	40540	NA
2	10.961	Toluene	BMB	91414	0.88	0.95	0.98	227965	47.00
3	11.664	DMF	BMB	10056949	96.59	1.00	2.90	28175	3.80
Total				10411091	100.0				

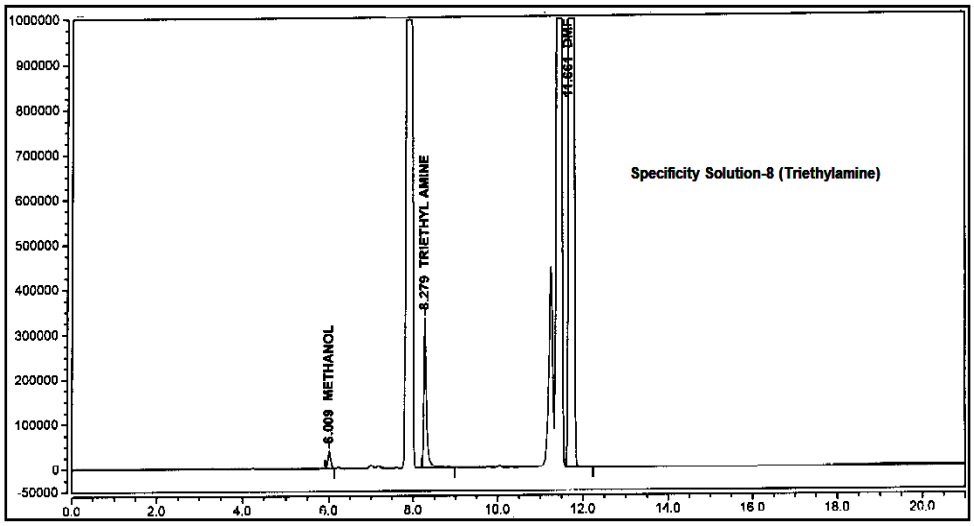

Figure 9:- Specificity solution-8, Triethyl amine.

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.009	Methanol	BMB	177461	1.51	0.51	1.03	40714	NA
2	8.279	Triethyl amine	BMB	1437111	12.28	0.71	1.73	104751	20.55
3	11.661	DMF	BMB	10094574	86.21	1.00	2.90	27933	17.79
Total				11709147	100.0				

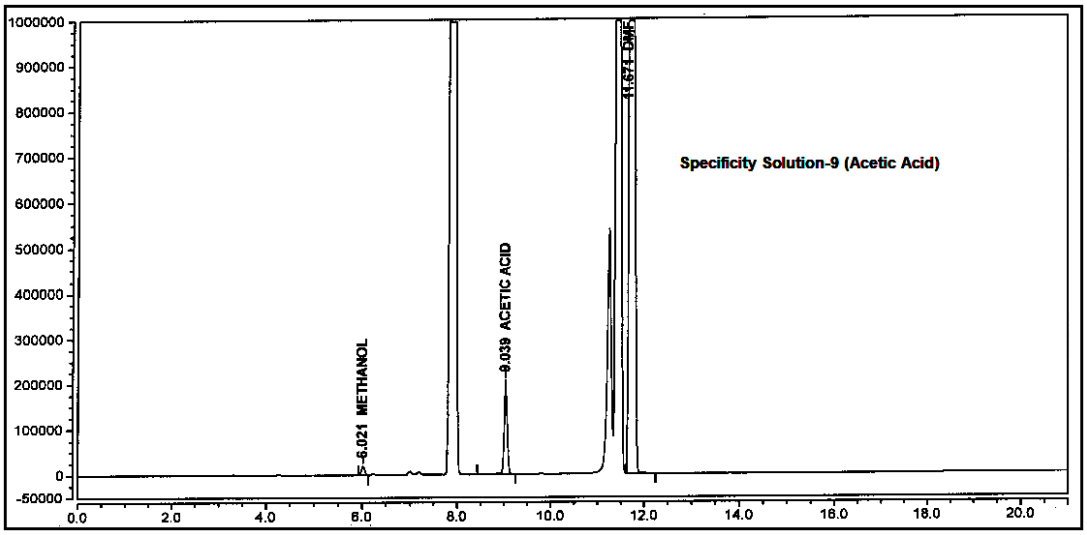

Figure 10:- Specificity solution-9, Acetic acid.

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.021	Methanol	BMB	92144	0.84	0.51	1.02	40888	NA
2	9.039	Acetic Acid	BMB	891370	8.02	0.77	0.98	107831	26.41
3	11.671	DMF	BMB	10119944	91.14	1.00	2.90	27759	13.51
Total				11103457	100.0				

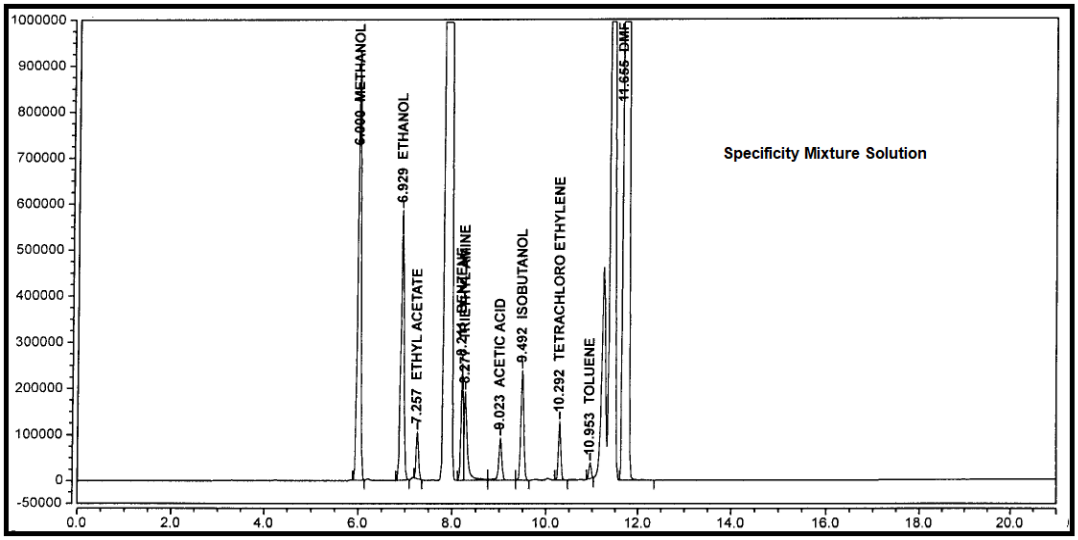

Figure 11:- Specificity Mixture solution.

Peak	RT (min)	Peak Name	Type	Area µV* sec	% Area	R.R.T	Asymmetry	Plates (EP)	Resolution (EP)
1	6.000	Methanol	BMB	4061147	19.48	0.51	1.03	41015	NA
2	6.929	Ethanol	BMB	2656138	12.74	0.59	1.03	52849	7.78
3	7.257	Ethyl Acetate	BMB	349422	1.65	0.62	1.12	100144	3.12
4	8.211	Benzene	BM	842939	4.02	0.70	NA	104125	9.90
5	8.277	Triethyl amine	M	907720	4.37	0.71	NA	NA	NA
6	9.023	Acetic Acid	MB	411204	1.99	0.77	0.97	110719	NA
7	9.492	Isobutanol	BMB	1009379	4.84	0.80	1.00	112430	4.27
8	10.292	Tetrachloro Ethylene	BMB	433996	2.08	0.88	1.03	205959	7.89
9	10.953	Toluene	BMB	116381	0.58	0.94	0.97	226728	7.28
10	11.655	DMF	BMB	10074555	48.29	1.00	2.92	27959	3.79
Total				20862675	100.0				

Limit of Detection (LOD):
A common method for measuring moisture content is the loss on drying (LOD) method. It is used to determine many key quality characteristics (Lokhande *et al., 2021*). It is based on the thermogravimetric principle, which heats a substance until it loses weight, i.e. it dries completely. First weigh the material and after drying it is obtained. The final weight loss is calculated and shows the moisture content of the sample.

Limit of Quantitation (LOQ):
The LOQ is the lowest level at which an analyte can be quantified with some degree of certainty. LOQ determination is similar to LOD determination, and although there are several accepted approaches, the method of calculating these figures of merit within a given method must be consistent *(Armbruster et al., 2008*). Because LOD and LOQ calculations are similar and one can be inferred from the other, LOD and LOQ are often reported together even when the method type does not require values for either (*Guo ,2008*). Limit of detection and Quantitation was determined by injecting low concentration of Acetic Acid in six replicate injections. The Limit of Detection and Quantitation value and relative standard deviation obtained for Acetic Acid is given below tables.

Table 3:- RSD of LOD & LOQ.

Inj.#	Area	
	LOD	LOQ
Inj.-1	21217	71861
Inj.-2	21902	71834
Inj.-3	22002	73033
Inj.-4	21391	72540
Inj.-5	21514	73967
Inj.-6	21419	74604
Mean	**21574**	**72973**
SD	**309.62**	**1129.0**
%RSD	**1.44**	**1.55**

Table 4:- Limit of Detection and Quantitation.

Parameter	Conc.(ppm)	Conc.(ppm) to test	Conc. (%)
LOD	25.49	509.8	10
LOQ	76.46	1529.2	30

Acceptance criteria:
RSD of six replicate injections of limit of detection solution for Acetic acid derivative should be NMT 30.0%. RSD of six replicate injections of Limit of Quantitation solution for Acetic acid derivative should be NMT 15.0%.

Linearity:
Linearity is the ability to obtain results that are directly proportional to the concentration of the analyte in the sample within a specified range, the distance between the upper and lower levels of the analyte. In the range of at least 80 to 120%, the test concentration is tripled. Estimated by the correlation coefficient of the linear curve, y-intercept, slope of the regression line, residual sum of squares *(Lokhande et al., 2018 & Lokhande et al., 2017).* The linearity of the GC-HS method was demonstrated by analysis Acetic Acid ranging from LOQ to 150 % (LOQ, 50%, 80%, l00%, 120% and 150%) of the specification limit.

T**able 5:-** Linearity for Acetic Acid Derivative.

Level	Conc.(ppm)	Area-1	Area-2	Area-3	Average
Level-I LOD	76.31	71602	72388	72865	72285
Level-II 50%	127.19	115876	116810	114987	115891
Level-III 80%	203.50	188095	191645	192431	190724
Level-IV 100%	254.38	248736	247977	242523	246412
Level-V 120%	305.25	298147	282045	289620	289937
Level-VI 150%	381.56	352814	362448	347953	354405

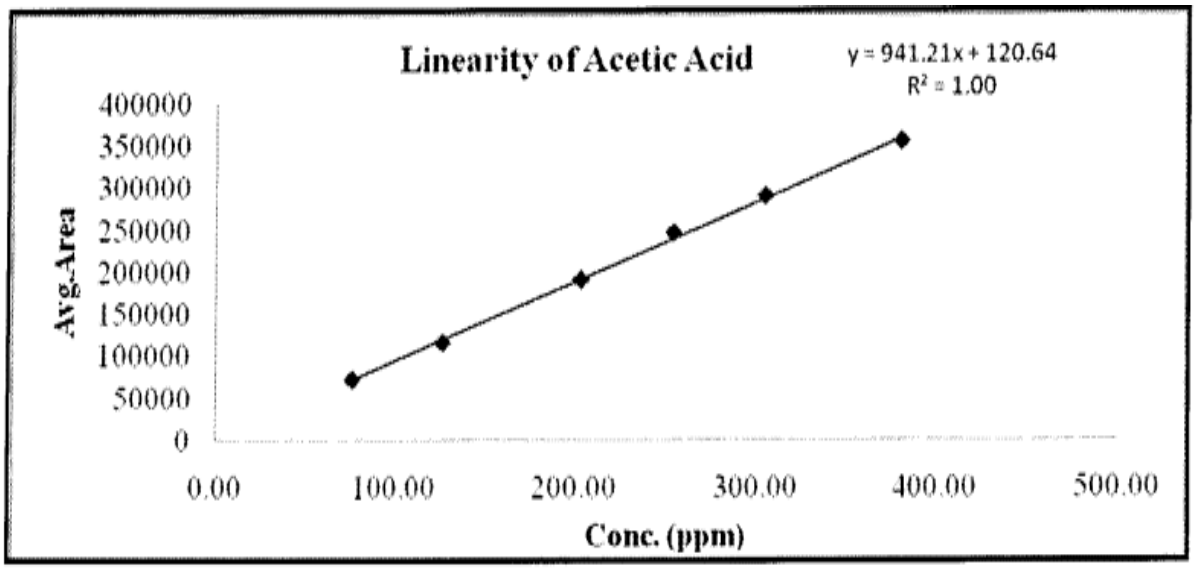

Figure 12:- Linearity plot for Acetic Acid Derivative.

Table 6:- Correlation coefficient (r) & % y –intercept.

Correlation coefficient (r)	%6 y-intercept
1.00	0.05

Acceptance criteria:
The plot of concentration in ppm versus average linear with a correlation coefficient (r) NLT 0.99 response of 100% standard solution.

Accuracy:
Accuracy is the degree of closeness between a measurement and its true value. Precision is the degree to which repeated measurements under the same conditions show the same results (*Wagh et al., 2017*). Prepared Flurbiprofen solution spiked with Acetic Acid in triplicate at LOQ, 50% and 150% level and 100% six determinations (in total l5 determinations) of the specification limit. The solutions were prepared individually in triplicate.

Table 7:- Accuracy.

Sample	Weight(mg)	Area	Amount (ppm)	Average
Test-01	100.63	987	20.98	21.95
Test-02	100.14	1073	22.91	

Table 8:- Recoveries for Acetic Acid Derivative.

Level	Test Spike(mg)	Amount added (ppm)	Area	Amount Found (ppm)	Amount recovered (ppm)	% Recovery	Mean % Recovery	SD	% RSD
Level-I LOQ	100.67	1521.81	70027	1487.57	1465.63	96.31	94.95	1.19	1.25
	100.59	1523.02	68684	1460.21	1438.27	64.44			
	100.60	1522.87	68441	1454.90	1432.96	94.10			
Level-II 50%	100.52	2540.13	115892	2465.55	2443.61	96.20	96.78	1.22	1.26
	100.60	2538.11	118261	2513.95	2492.01	98.18			
	100.49	2540.89	115617	2460.44	2438.50	95.97			
Level-IV 100%	100.35	5088.87	239664	5107.39	5085.45	99.93	99.91	0.32	0.32
	100.56	5078.24	238825	5078.88	5056.94	99.58			
	100.29	5091.91	240361	5125.30	5103.36	100.22			
Level-V 150%	100.56	7617.36	359684	7649.08	7627.14	100.13	100.07	0.27	0.27
	100.35	7633.30	358483	7639.49	7617.55	99.79			
	100.51	7621.15	360379	7667.67	7645.73	100.32			

Acceptance criteria:
The recovery obtained for Acetic acid derivative should be in the range of 70 % to l30% at LOQ. RSD of the o/o recovery obtained at LOQ should be NMT 15.0%. The recoveries obtained for Acetic Acid derivative should be in the range of 80% to l20 %.at 50Yo,100%o and 150% levels. RSD of the recoveries obtained at 50%, 100% and 150% levels should be NMT 10.0%.

Precision:
Precision analysis is used to refine the existing precision metadata definition for selective columns (for example, data type numeric columns) based on the actual data values that are present in the column *(Zate et al., 2017)*.
a) *System Precision*: The two most important elements of a chromatographic test method are accuracy and precision. Accuracy is a measure of the closeness of the experimental value to the actual amount of the substance in the matrix *(Rathod et al., 2015)*. Precision measures of how close individual measurements are to each other. System precision was determined by performing six replicate injections of standard solution per method of analysis and analyzed. System precision result is listed below table.

Table 9:- System precision.

Injection number	Area
1	230648
2	237544
3	241328
4	239907
5	241506
6	241839
Mean	**238795**
SD	**4294.34**
RSD	**1.80**

Acceptance criteria:
RSD for the area of Acetic acid derivative from the six replicate injections of standard solution should be NMT 10.0%

Method precision:
Precision of a method is the degree of agreement among individual test results when the procedure is applied repeatedly to multiple samplings. Precision is measured by injecting a series of standards or analyzing series of samples from multiple samplings from a homogeneous lot *(Muhammad et al., 2012 & Dong, 2006*). Prepared six

different preparations of Flurbiprofen spiked with Acetic Acid at specification level (100%) and analysed as per the method of analysis for determining the method precision.

Table 10:- Results in ppm of Acetic Acid for Method precision.

Level	Test Spike(mg)	Amount added (ppm)	Area	Amount Found (ppm)	Amount recovered (ppm)	Mean	SD	% RSD
100 %	100.35	5088.87	239664	5017.39	5085.45	5105.71	35.33	0.68
	100.56	5087.24	238825	5078.88	5056.94			
	100.29	5091.91	240261	5125.30	5103.36			
	100.53	5079.76	240909	5124.73	5102.79			
	100.45	5083.80	243463	5183.18	5161.24			
	100.34	5089.37	241474	5146.47	5124.53			

Acceptance criteria: RSD of amount recovered in ppm for Acetic acid derivative obtained should be NMT 10.0%.

Intermediate precision:

Intermediate precision is the accounts for intra-laboratory variations, accounting for different days, different analysts or different instruments (*Q2 (R1), 2014*). In fact, the repeatability was performed three times. Therefore, a preliminary determination of Intermediate precision can be obtained from repeatability tests. The second and third measurements are obtained by repeating the experiment on two consecutive days. A solution of Flurbiprofen spiked with Acetic Acid at specification level (100%) prepared six times (six individual preparation) and analyzed as per the analytical method for determining the intermediate precision by different analyst, day, instrument and column.

Table 11:- System suitability

Injection Number	RT (min)	Area
Inj.-1	9.548	528
Inj.-2	9.547	559
Inj.-3	9.548	578
Inj.-4	9.542	493
Inj.-5	9.539	455
Inj.-6	9.540	472
Average	**9.544**	**514**
SD	**0.000**	**49.13**
%RSD	**0.00**	**9.55**

Table 12:- Acetic Acid in-test as such.

Sample	Weight (mg)	Area	Amount Found (ppm)	Average (ppm)
Test-1	100.52	Not detected	Not detected	Not detected
Test-2	100.57	Not detected	Not detected	

Table 13:- In ppm of Acetic Acid Derivative for intermediate precision.

Level	Test Spike(mg)	Amount added (ppm)	Area Test Spike	Amount Found (ppm)	Amount recovered (ppm)	Mean	SD	% RSD
100 %	100.98	5038.14	480	4704.88	4704.88	4942.99	194.21	3.92
	100.33	5070.78	493	4863.61	4863.61			
	100.51	5061.70	500	4923.83	4923.83			
	100.06	5084.46	534	5282.30	5282.30			
	100.56	5059.17	518	5098.55	5098.55			
	101.06	5034.15	489	4789.30	4789.30			

Table 14:- Cumulative RSD for intermediate precision.

Details	Test number	Amount Recovered (ppm)
Analyst -1 Instrument-RDS/AMD/GC-03 Column No-AMD/ lCAP /073 (Method Precision)	Test-1	5084.44
	Test-2	5055.93
	Test-3	5103.35
	Test-4	5101.78
	Test-5	5161.25
	Test-6	5124.52
Analyst-2 Instrument-RDS/AMD/GC-05 Column No.-AMD/ AP/ 069 (Intermediate Precision)	Test-1	4704.89
	Test-2	4863.60
	Test-3	4922.84
	Test-4	5281.29
	Test-5	5097.54
	Test-6	4788.29
Mean		5023.72
SD		168.21
% RSD		3.34

Acceptance criteria:
RSD of area of Acetic Acid derivative of six standard solution injections should be NMT 10.0%. RSD of amount recovered in ppm for Acetic Acid derivative obtained should be NMT 10.0%. Cumulative RSD of amount recovered in ppm for Acetic Acid derivative obtained from two set (twelve determinations) should be NMT 10.0%.

Conclusions:-

Validated the GCHS method for the determination of Acetic acid content in Flurbiprofen and demonstrated that the method is appropriate for its intended use. The report is applicable only for the determination of Acetic acid content in Flurbiprofen as per the method of analysis. Acetic acid was used as solvent in manufacturing process of Flurbiprofen. In house GCHS method has been developed for the determination of Acetic Acid in Flurbiprofen. The method validated as per the current ICH guidelines in order to give evidence of its reliability and suitability. Determined Validation data has compiled based on the evaluation of chromatograms. Validation shall be repeated whenever there is any significant change in the method used for the determination of Acetic acid in Flurbiprofen. This can be useful for routine in process quality control and simultaneous estimation of Flurbiprofen. The proposed method was found to be simple, rapid, economical, accurate and precise. Based on the results obtained, validation report compiled and concludes suitability of analytical method. the summary of as below;

System suitability	Component	% RSD		
	Acetic Acid Derivative	3.29		
Specificity	Peak due to Acetic acid derivative is adequately resolved from other solvents and from diluent.			
Limit of Detection and Quantitation	Solution	Acetic Acid Derivative		
		Conc. (ppm)	Conc. (ppm) to test	% RSD
	LOD	25.49	509.8	1.44
	LOQ	76.46	1529.2	1.55
Linearity & Range	Correlation coefficient (r)		%o y-intercept	
	1.00		0.05	
Accuracy	Recovery obtained is between 94.10% to 96.31% at LOQ level. RSD of recovery at LOQ level is l.25%. Recovery obtained is between 95.97% to 100.32% at 50%,100% and 150% level. RSD of recovery at 50% to 150% level is between A.27 to 1.26.			
Precision				
System precision	RSD of area is 1.80 %			
Method precision	RSD of amount recovered in ppm is 0.69 %			
Intermediate Precision	Cumulative RSD of amount recovered in ppm is 3.35 %			

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Conflict of Interest:
We are authors declare that, there is no conflict of interest.

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