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"VALIDATION OF STABILITY INDICATING HIGH PERFORMANCE LIQUID CHROMATOGRAPHIC METHOD FOR DETERMINATION OF ASSAY OF MESALAMINE DRUG IN THE PHARMACEUTICALS TABLET FORMULATIONS USING SODIUM BENZOATE AS AN INTERNAL STANDARD"

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ABSTRACT
Mesalamine is an anti-inflammatory drug used to treat inflammation of the digestive tract (Crohn's disease) and mild to moderate ulcerative colitis. Validation of stability indicating Simple, Specific, Precise, Accurate, Linear, Rugged, Robust High Performance Liquid Chromatographic method of analysis for determination of assay of Mesalamine drug in the pharmaceuticals tablet formulations using Sodium benzoate as an internal standard was performed. The assay was accomplished using a mixture of Methanol and Buffer solution in the volume ratio of 65:35 v/v as mobile phase on Hibar RP-18e, 250 mm x 4.6mm, 5µ as chromatographic column at a flow rate of 1.000 ml per min and a wavelength of 240 nm with a UV detector. The temperature of auto injector and column oven was 10^0C and 30^0C receptively. The Injection volume kept as 10 µL. Linearity of the analytical method was evaluated at concentration range of 5.0002 µg/ml to 339.9986 µg/ml with Correlation coefficient (r) value more than 0.999. The LOD and LOQ were 1.4558µg/mL and 4.4116µg/mL respectively. The retention time found to be 6.17 min for Mesalamine and 4.21 min for internal standard respectively. Specificity, Method Precision, System Precision, Ruggedness, Robustness, Recovery, Stability of analytical solution, Filter paper selection study, Stress testing (Force Degradation) at various conditions were performed as per the ICH (Q2) recommendations. All the results were found with in acceptance criteria.

KEYWORDS: Mesalamine, Sodium benzoate, High Performance Liquid Chromatographic, Force degradation studies, Assay.

INTRODUCTION
Mesalamine is an anti-inflammatory drug used to treat inflammation of the digestive tract (Crohn's disease) and mild to moderate ulcerative colitis. Mesalamine is a bowel-specific aminosalicylate drug that is metabolized in the gut and has its predominant actions there, thereby having fewer systemic side effects. The chemical name is 5-amino-2-hydroxybenzoic acid. The molecular formula for Mesalamine is $C_7H_7NO_3$. The molecular weight of Mesalamine is 153.14. Mesalamine is light tan powder. Mesalamine is soluble in water (0.844 mg/mL), methanol, solubility of Mesalamine is increased with pH 2.2 to pH 5.5. The pKa of Mesalamine is 2.02 and 5.87.[1,6]

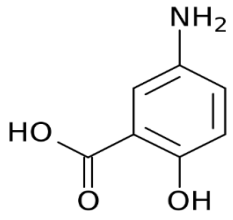


Figure 1: Chemical structure of Mesalamine.

Sodium benzoate is an fungistatic compound that is broadly used for preservation of food such as salad dressings (vinegar), carbonated drinks (carbonic acid), jams and fruit juices (citric acid), pickles (vinegar), and condiments. It is conjugated to GLYCINE in the liver and excreted as hippuric acid. As the form, Sodium benzoate is sodium salt of benzoic acid used as a

treatment for urea cycle disorders due to its ability to bind amino acids. This leads to excretion of these amino acids and a decrease in ammonia levels. As per the recent research sodium benzoate may be useful as an add-on therapy (1 gram/day) in schizophrenia. Total Positive and Negative Syndrome Scale scores dropped by 21% compared to placebo. The molecular formula is $C_7H_5O_2Na$. The molecular weight of Sodium benzoate is 144.10. Sodium benzoate is White, odorless or nearly odorless granules, crystalline powder and has a pKa of 4.19. Sodium Benzoate is soluble in water and organic solvents such as methanol.[1,6]

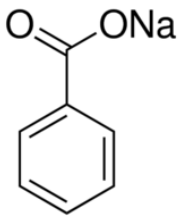


Figure 2: Chemical structure of Sodium benzoate.

While Reviewing Literature for analytical method of analysis it was observed that many methods have been reported for determination of Mesalamine in combination and individually[7,22] but none of the reported HPLC methods have not been validated using internal standard to compensate any processing related and method related variability. Most of the published method[7,22] not performed stability-indicating studies (Acid, Alkali, Peroxide, Thermal, Photolytic, Humidity degradation,) which are mandatory as per the ICH (Q2) recommendations.

The main objective of the work is to develop and validate stability indicating HPLC method[23,26] of analysis which is Simple, Specific, Precise, Accurate, Linear, Rugged, Robust etc. for determination of assay of Mesalamine drug in the pharmaceutical tablet formulations using Sodium benzoate as an internal standard.

MATERIAL AND METHODS

Instrumentation

Shimadzu Prominence HPLC system equipped with dual pump, SIL-HTc auto-sampler with cooler, column oven, variable wavelength UV detector and a data acquisition system (Lab Solution Software) were used for the determination of assay of Mesalamine drug in the pharmaceutical tablet formulations using Sodium benzoate as an internal standard.

Reagents and Materials

The reagents used during analysis Methanol [HPLC Grade], Water [Milli-Q /HPLC Grade], Tetra ammonium Hydrogen Sulfate [AR Grade], Sodium acetate trihydrate [AR Grade], Sodium Hydroxide [GR Grade], Mono Potassium phosphate [AR grade], Formic Acid [LR grade], Mesalamine and Sodium benzoate were used obtained from Wockhardt Pharmaceutical limited. Fixed dose tablets containing 800 mg of Mesalamine of Sun Pharmaceutical Industries Ltd. was purchased from Local medical, Aurangabad (Maharashtra).

Analytical solutions

A mixture of 3.4 g of Tetra ammonium Hydrogen Sulfate and 1.4 g of Sodium acetate trihydrate into 1000 mL Milli-Q water was prepared as a buffer solution and used in mobile phase. A mixture, Methanol and Buffer solution was prepared in the volume ratio of 65:35 v/v respectively, as mobile phase. A mixture of 6.8 g of Monopotassium phosphate and 4.0 g of Sodium hydroxide pellets into 1000 mL Milli-Q water was prepared and used as a diluent for preparation of sample solution. Stock solutions having concentrations approximately, 499.9980 µg/mL of Mesalamine in 0.1% formic acid in methanol and 10000.8360 µg/mL of Sodium benzoate in methanol were prepared and solutions were filtered through 0.45µm nylon membrane filter with discarding first 2 mL of the filtrate before use. The solution of Sodium benzoate was used as internal standard dilution solution during various experiments performed in an analytical method validation and assay calculations of pharmaceutical formulation.

Standard solution having concentrations approximately, 100.000 µg/ml of Mesalamine and 62.5052 µg/mL of Sodium benzoate in mixture were prepared in mobile phase and use as a reference solution for related activities and system suitability. Filter the solution through 0.45µm nylon membrane filter with discarding first 2 mL of the filtrate before use.

Sample solution having concentrations 100.00 µg/ml of Mesalamine and 62.5052 µg/mL of Sodium benzoate was prepared in mobile phase by dissolving a quantity of powder equivalent to Strength of 800 mg of Mesalamine and use as a sample solution for related activities. Filter the solution through 0.45µm nylon membrane filter with discarding first 2 mL of the filtrate before use.

RESULT AND DISCUSSION

Method development

Primarily, numerous trials for optimization of method was performed using different mobile phases composition, different ratios of organic to buffer, different organic solvents, different buffer with different pH, different stationary phases, different internal standards and variable chromatographic settings in an effort to achieve the finest peak resolution and separation between Mesalamine and internal standard as depicted in Figure No.3.

A summarized chromatographic condition mentioned as follows:

Mobile phase: Methanol, Buffer solution (65:35v/v)
Rinsing Solution: Methanol: Mill-Q water (65:35v/v)
Chromatographic Column: Hibar RP-18e, 250 mm x 4.6mm, 5µ
Wavelength: 240 nm

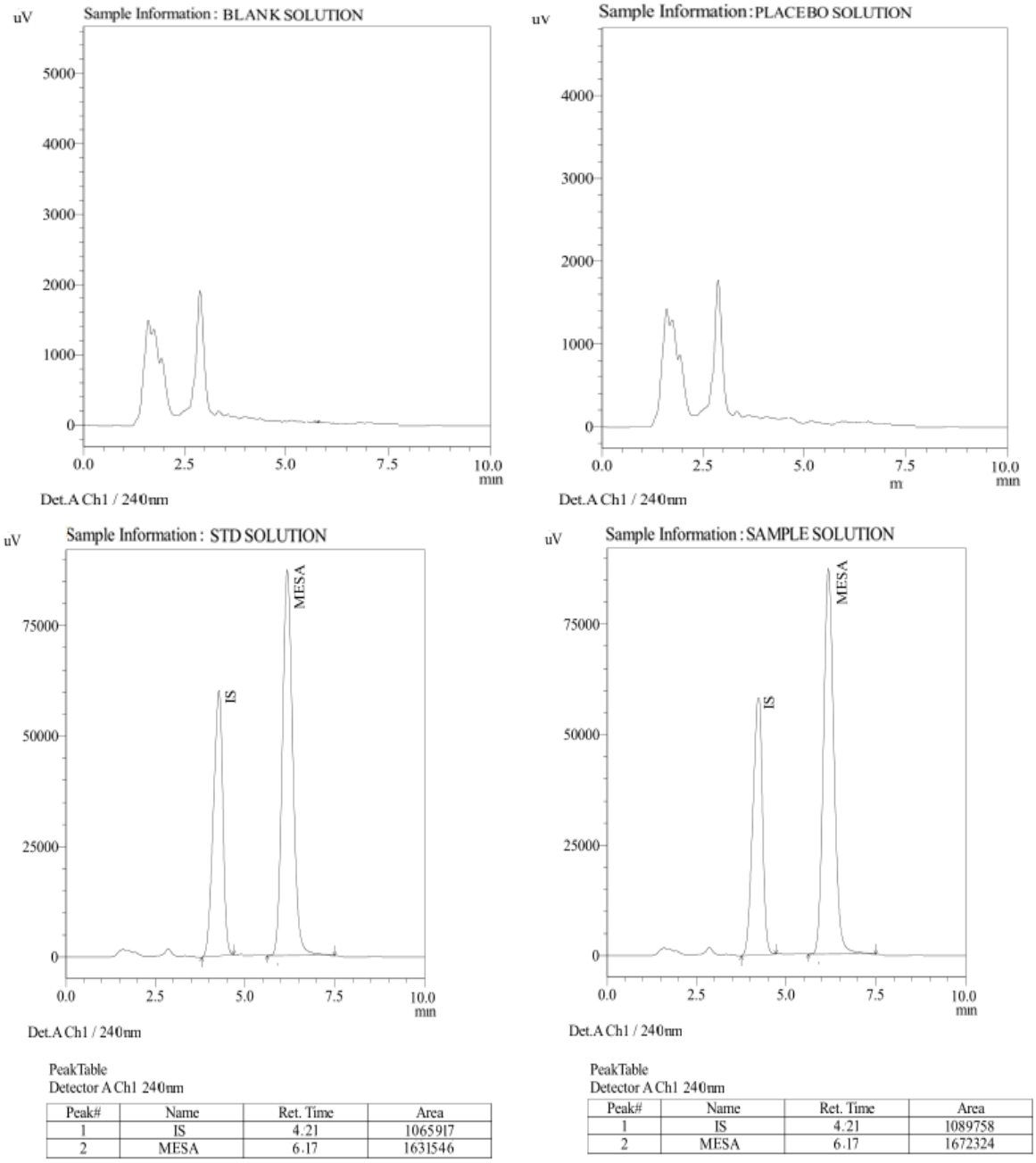
Column Oven Temperature:	30 ^{0}C
Sample cooler Temperature:	10 ^{0}C
Flow rate:	1.000 ml per minute
Injection Volume:	10 µl
Run Time:	10 minute
Retention Time (minute):	Mesalamine - 6.17
	Sodium benzoate - 4.21

Analytical method validation

The Analytical method was optimized and validated in accordance with the current ICH guidelines and recommendations by means of a vision to accomplish Simple, Specific, Precise, Accurate, Linear, Rugged, Robust method.[23,26]

Specificity

For the evaluation of specificity; Blank solution, placebo solutions, sample solution, standard solution in triplicate were injected into HPLC system. No interference was observed from blank solution and placebo at the retention time of chromatographic peak of Mesalamine and internal standard. Peak purity passes (purity angle was less than purity threshold) for Mesalamine and % assay difference with respect to method precision found to be 0.10%. The typical chromatograms of various samples under optimized HPLC conditions depicted in Figure No.3.



PeakTable
Detector A Ch1 240nm

Peak#	Name	Ret. Time	Area
1	IS	4.21	1065917
2	MESA	6.17	1631546

PeakTable
Detector A Ch1 240nm

Peak#	Name	Ret. Time	Area
1	IS	4.21	1089758
2	MESA	6.17	1672324

Figure 3: Typical chromatograms of Blank solution, Placebo solution, Sample solution & standard Solution.

System Precision

Six replicates injections of standard solution injected in to the HPLC system and the chromatograms and area ratio of Mesalamine to the Sodium benzoate recorded. For Mesalamine Theoretical plates and Tailing factor found to be 9352 and 1.50 respectively. %RSD for area ratio of Mesalamine to the Sodium benzoate of six replicate injections of standard solution found to be 0.10% implies that system is précises as tabulated in Table No.1.

Table No. 1: Result of System precision for Mesalamine.

Injection No.	Area ratio (Mesalamine to Sodium benzoate)
1	1.5307
2	1.5334
3	1.5349
4	1.5335
5	1.5313
6	1.5320
Mean	**1.5326**
Standard Deviation	**0.00157**
% R.S.D.	**0.10**

Method Precision

For the evaluation of Method precision of the analytical method, six samples from homogenous mixture of single batch were prepared as per the test procedure of methodology and analyzed on HPLC system. %RSD for % assay of Mesalamine of six samples found to be 0.25% as tabulated in Table No.2.

Table No. 2: Result of Method precision for Mesalamine.

Sample No.	% Assay of Mesalamine
1	99.3
2	99.6
3	99.7
4	100.0
5	99.8
6	99.9
Mean	**99.7**
Standard Deviation	**0.25**
% R.S.D.	**0.25**

Method Ruggedness

The ruggedness of the method was evaluated through analysis of six samples from a homogenous mixture of single batch by different analyst by using different column, different system and on different day. %RSD for % assay of ruggedness samples found to be 0.14% and Overall %RSD of ruggedness and method precision samples found to be 0.19% as tabulated in Table No.3.

Table No. 3: Result of Ruggedness for Mesalamine.

Sr. No.	Mesalamine	
	% Assay of Mesalamine Method precision	% Assay of Mesalamine Ruggedness
1	99.3	99.8
2	99.6	99.7
3	99.7	99.6
4	100.0	99.9
5	99.8	99.5
6	99.9	99.7
Mean	**99.7**	**99.7**
Standard Deviation	**0.25**	**0.14**
% R.S.D.	**0.25**	**0.14**
Overall Mean	**99.7**	
Overall S.D.	**0.19**	
Overall R.S.D.	**0.19**	

Accuracy (Recovery)

Accuracy of the analytical method was evaluated at a known concentration of Mesalamine at about 50%, 100% and 150% of test concentration of sample solution and 50% (1X Blend) and 150% (3X Blend) was calculated. % accuracy at individual level and overall average of % Recovery at all level for Mesalamine found to be in the range 99% to 101% as tabulated in Table No.4.

Table No. 4: Result of Recovery for Mesalamine.

Spike level in %	Mesalamine			
	% Recovery	Mean	SD	% RSD
50% (Assay)	99.7	99.5	0.29	0.29
	99.2			
	99.7			
100% (Assay)	99.4	99.7	0.25	0.25
	99.7			
	99.9			
150% (Assay)	99.5	99.7	0.17	0.17
	99.8			
	99.8			
50% (1X Blend)	99.4	99.3	0.10	0.10
	99.2			
	99.3			
150% (3X Blend)	100.2	99.8	0.35	0.35
	99.8			
	99.5			
Overall Mean	99.6			
Overall S.D.	0.28			
Overall % R.S.D.	0.28			

Linearity

For the evolution of the linearity of the analytical method, a standard dilution of Mesalamine in a concentration range of 5.0002 µg/ml to 339.9986 µg/ml were prepared as per the test procedure of methodology and analyzed on the HPLC system.

Correlation coefficient (r) value for Mesalamine using a regression equation with a 1/ (concentration^2) of weighting factor was calculated over above mentioned range.

Lower limit of Detection (LOD) and Lower limit of Quantification (LOQ) calculated using following formulas.

Limit of detection (LOD) =3.3 X S.D. of Y intercept / Slope of the calibration curve.

Limit of Quantification (LOQ) =10 X S.D. of Y intercept / Slope of the calibration curve.

The LOD and LOQ were found to be 1.4558 µg/ml and 4.4116 µg/ml respectively. Correlation coefficient (r) value found more than 0.9999.

The linearity plot depicted in Figure No.4 and Results were tabulated in Table No.5.

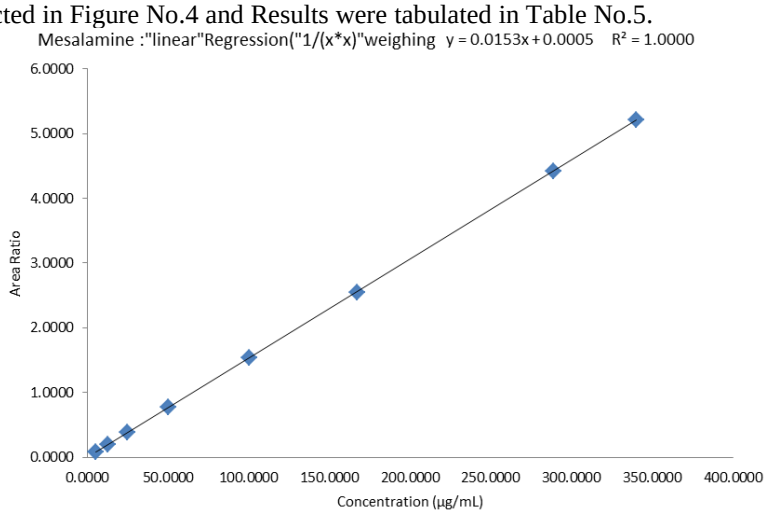


Figure 4: Linearity plot for Mesalamine.

Table No. 5: Result of Linearity for Mesalamine.

Sample no.	Mesalamine	
	Concentration in µg/mL	Area Ratio
1	5.0002	0.0781
2	12.5006	0.1936
3	25.0012	0.3811
4	50.0023	0.7712
5	100.0046	1.5328
6	166.8968	2.5442
7	288.9988	4.4189
8	339.9986	5.2141
Slope	**0.0153**	
Intercept	**0.0005**	
CC (r)	**1.0000**	

The results of the linearity confirmed that an excellent correlation was exists between area ratio and concentration of drug within the specified concentration range.

Stability in analytical solution

For the evolution of stability in analytical solution; freshly prepared standard solution and sample solution injected on the HPLC system at initially and different time intervals up to 53 hours and 52 hours respectively and the results of standard solution and sample solution were recorded. Absolute % difference and similarity factor were calculated.

For sample solution; absolute % difference between the assay of initial result and assay obtained at different time intervals found to be in the range 0.10% to 0.20%.

For standard solution; similarity factor between the initial result and results obtained at different time intervals found to be in the range of 99.3% to 99.6%.

Filter paper study

Filter paper study was performed to measure the analysis impact of filter paper used during various experiments of analytical method validation. For the evolution of the filter paper study of the analytical method, standard solution was prepared as per test procedure of methodology and distributed the standard solution in two different portions. One portion centrifuged at 4000 rpm for 5 minutes and second portion was filter through 0.45-µm nylon membrane filter with discarding first 2mL of the filtrate and all the samples were analyzed on HPLC system.

Similarity factor between mean average area ratio of as such standard solution and filtered standard solution found to be 100.3. Absolute difference between average % assay of centrifuged sample solution and filtered sample solution found to be 0.10%.

Form the results it was concluded that the 0.45-µm nylon membrane filter with discarding first 2mL of the filtrate is suitable for the determination of Assay of Mesalamine in tablet formulation.

Forced degradation study

Forced degradation study was performed by treating sample solution of tablet containing 800 mg Mesalamine under acidic, basic, peroxide, thermal, photolytic and humidity conditions, no significant degradation of the Mesalamine observed under treated stress condition as tabulated in Table No.6.

Table No. 6: Results of Force degradation for Mesalamine.

Degradation Condition	% Degradation
Acid Treated	0.8
Alkali Treated	0.5
Peroxide Treated	1.0
Thermal Treated	0.3
Photolytic Treated	0.1
Humidity Treated	0.0

Method robustness

Robustness of the analytical method was evaluated by accomplishment of analysis under marginally changed in the chromatographic method of analysis such as change in detection wavelength, change in flow rate, change in composition of the mobile phase and change in column oven temperature and the assay results were compared with the assay result of method precision i.e. with finalized chromatographic conditions. The analytical method used is robust for change in flow rate, change in column oven temperature, change organic component of mobile phase and change in wavelength. Overall %RSD between % assay at original parameters and changed parameters were calculated as tabulated in Table No.7.

Table No. 7: Result of robustness for Mesalamine.

Sr. No	Method precision	Minus Flow	Plus Flow	Minus Temp	Plus Temp	Minus Organic comp. (MeOH)	Plus Organic comp. (MeOH)	Minus Wavelength	Plus Wavelength
1	99.3	99.9	99.8	99.9	99.3	99.2	99.3	99.3	99.4
2	99.6	99.9	99.7	99.8	99.7	99.5	99.1	99.5	99.2
3	99.7	99.6	99.9	99.9	99.4	99.3	99.4	99.6	99.3
4	100.0	Not applicable							
5	99.8								
6	99.9								
Overall mean		99.7	99.7	99.8	99.6	99.6	99.6	99.6	99.6
Overall SD		0.22	0.21	0.21	0.25	0.28	0.31	0.24	0.29
Overall %RSD		0.22	0.21	0.21	0.25	0.28	0.31	0.24	0.29

Range

From the analytical procedure data of precision, accuracy and linearity, the range of the analytical method used for determination of assay of Mesalamine drug in the pharmaceutical tablet formulations using Sodium benzoate as an internal standard was tabulated in Table No.8.

Table No. 8: Range for Mesalamine.

Name of Analyte	Concentration (µg/mL)
Mesalamine	5.0002 µg/ml to 339.9986 µg/ml

Analysis of Marketed Products

The potency test of marketed tablet products were performed after the complete validation of the method for determination of assay of Mesalamine drug in the pharmaceutical tablet formulations using Sodium benzoate as an internal standard was performed by the proposed validated method.

The potency of tested brands was found to be within the limit of 98.00-102.00%. The results are tabulated in Table no. 9.

Table No. 9: Potency of Marketed Products for Mesalamine.

Sr.No.	Mesalamine			
	Brand name code	Label Claimed (mg)	Amount found (mg)	Potency (%)
1	MESA(A)	800	798	99.75
2	MESA(B)	800	799	99.88

CONCLUSIONS

This is the first reported High Performance Liquid Chromatographic method developed used for determination of assay of Mesalamine drug in the pharmaceuticals tablet formulations using Sodium benzoate as an internal standard was stability indicating as recommended by ICH guidelines and validated for Specificity, System precision, Method precision, Ruggedness, Robustness, Accuracy etc. The present analytical method has a widespread linear concentration range augmenting its applicability to different strength of Mesalamine tablet formulations. The chromatographic method may also be applied for estimation of analyte in plasma, serum, urine after using appropriate sample extraction technique. Thus the method is Simpler, Accurate and Economical as compare to the previous methods.

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