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ULTRAPERFORMANCE LIQUID CHROMATOGRAPHY [UPLC]

Hande S.G., Walunj N.B., Jadhav P.S., Gaikwad A.V., Tare H.L., Dama G.Y.
SGMSPM's Sharadchandra Pawar College of Pharmacy, Otur, Pune, M.S., India 400050.

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For Correspondence:

Sonali Hande
SGMSPM's
Sharadchandra Pawar
College of Pharmacy, Otur,
Pune, M.S., India

ABSTRACT

Ultra Performance Liquid Chromatography, or UPLC be extended to new limits, termed Ultra Performance term relatively new technique giving new possibilities in liquid chromatography, especially concerning decrease of time and solvent consumption. The key focus of the pharmaceutical or chemical industries is to reduce the cost involved in the development of new drugs and to improve the selectivity ,sensitivity and resolution for their detection .the purpose can now resolved by the separation method called UPLC which is modified HPLC method comprising of highest pressure and small sized particles(less than 2 micrometer). UPLC chromatographic system is designed in a special way to withstand high system back-pressures. The quality control analyses of various pharmaceutical formulations are transferred from HPLC to UPLC system. The separation on UPLC is performed under very high pressures (up to 100 MPa) but it has no negative influence on analytical column or other components of chromatographic system. Separation efficiency remains maintained or is even improved by UPLC. This review introduces the theory of UPLC, and summarizes some of the most recent works.

INTRODUCTION

UPLC refers to Ultra Performance Liquid Chromatography. It improves in three areas: chromatographic resolution, speed and sensitivity analysis. It uses fine particles and saves time and reduces solvent consumption. UPLC comes from HPLC. UPLC is of materials used for packaging is used in stimulating the separation. The Casual ideology of this used in many laboratories all over the world .One of the main advantage of this technique is growth and development is due to the advancement. advancement is governed by what is called the Van Demeter equation. This Technology takes full benefit of Chromatographic principles to encourage separations utilizing columns chock full of tinier particles and/or superior flow rates for higher speed with exceptional resolution and excellent sensitivity. Today, because of in vivo doses or low sample size doses, new technology using narrow, high density columns boasting higher resolution and more precise sensitivities, Speed and precision became much higher and could be expected when using UPLC. What is UPLC? The term UPLC, meaning "Ultra Performance Liquid Chromatography," was introduced by Waters Corporation when they introduced their Acquity LC system. The biggest change was the use of sub-2 um particles, which were operated at higher flows and pressures than a conventional system.

UPLC is Defined as the new category of analytical separation technique or science retains the practicality and principles of HPLC while increasing the overall interlaced attributes of speed, sensitivity, and resolution.

To be extended new limits, termed Ultra Performance Liquid chromatography, According to the van Deemter equation, as the particle size decreases to less than 2.5 m, not only is there a significant gain in efficiency, but the efficiency does not diminish at increased flow rates or linear velocity

$$H=A+B/V+Cv……..(I)$$

Where,H represents height equivalent to the theoretical plate (HETP), A,B&C are the constants and V is flow rate of the carrier gas .

USE OF THE UPLC SYSTEM:

Elevated temperature chromatography also allows the high flow rates by lowering the velocity of the mobile phase, which significantly reduces he back pressure monolithic coulumns contain a polymerized pourous support structure that provides lower flow rates.

INSTRUMENTATION:

1] Sample injector

2] UPLC Columns

3]Detectors

[Figure 1]UPLC SYSTEM

1] SAMPLE INJECTION:

In UPLC, sample introduction is critical. Conventional injection valves, either automated or manual, are not designed and hardened to work at extreme pressure. To protect the column from

extreme pressure fluctuations, the injection process must be relatively pulse-free and the swept volume of the device also needs to be minimal to reduce potential band spreading. A fast injection cycle time is needed to fully capitalize on the speed afforded by UPLC, which in turn requires a high sample capacity. Low volume injections with minimal carryover are also required to increase sensitivity.

2] UPLC COLUMNS

Resolution is increased in a 1.7 micrometer particle packed in column because efficiency is better. Separation of the components of a sample requires a bonded phase that provides both retention and selectivity. Four bonded phases are available for UPLC separations:

ACQUITY UPLC™ BEH C_{18} and C_8 (straight chain alkyl columns),

ACQUITY UPLC BEH Shield RP_{18} (embedded polar group columns)

ACQUITY UPLC BEH Phenyl (phenyl group tethered to the silyl functionality with a C_6 alkyl).

BEH C8 column,

- BEH shield RP 18 columns
- BEH amide columns
- BEH HILIC columns
- BEH phenyl columns
- BEH 130 & BEH 300 columns
- UPLC CSH PHENYL-HEXYL columns
- BEH 125, BEH 200,BEH 450 SEC columns
- BEH 300 c4 columns
- BEH glycan columns

UPLC OST C 18 columns

Each column chemistry provides a different combination of hydrophobisity silanol activity, hydrolytic stability and chemical interaction with analytes.

Phases of UPLC Columns:

ACQUITY UPLC BEH C_{18} and C_8 columns are considered the universal columns of choice for most UPLC separations by providing the widest pH range. [9,10,11,12]

Detector:-For UPLC detection, the tunable UV/Visible detector is used.

Spectrophotometric detectors in the ultraviolet (UV)-visible range for HPLC are used. more frequently than any other by analysts in general, so they are relatively inexpensive and tend to be one of the first to which lipid analysts have access. Detectors are constructed specifically for HPLC use with a cell volume of about 8 microlitres are recommended (as opposed to UV

spectrophotometers with a flow-cell as an optional extra), and only those affording continuously variable wavelengths are of much value to lipid analysts.

UV Detector:

UV detectors can sometimes give Detectors for HPLC of lipids with special reference to evaporative light-scattering detection great selectivity and sometimes sensitivity in the analysis of specific compounds, and they are relatively insensitive to changes in ambient temperature or the flow-rate of the mobile phase. While they can be used in gradient elution applications on occasion, base-line drift can be trouble sometime. A detector cell can easily become contaminated in use, although this may not be immediately obvious.

Comparison between UPLC and HPLC		
Characteristics	**HPLC**	**UPLC**
Particle size	3 to 5m	Less than 2m
Maximum back pressure	35-40 MPa	103.5 MPa
Analytical column	Alltima C_{18}	Acquity UPLC BEH C_{18}
Column dimensions	150 X 3.2 mm	150 X 2.1 mm
Column temperature	30 degree Cel.	65 degree Cel.
Injection volume	5L (Std. In100% MeOH)	2L (Std.In100% MeOH)

Table 1: Comparison between UPLC and HPLC:

TYPES OF DETECTORS:

1)TUV(tunable ultra violet) detector

2)PDA(photo diode array) detector

3)ELS(avoprative light scattering) detector

4)FLR(fluorescence) detector

COMPARATIVE ACCOUNT OF COLUMN OF HPLC AND UPLC:-

A column tube and fittings must contain the chromatographic Packing material (stationary phase) that is used to effect a separation. It must withstand backpressure created both during manufacturing and in use. Also, it must provide a well-controlled (leak-free, minimum volume and zero-dead-volume) flow path for the sample at its inlet and analyte bands at its outlet and be

chemically inert relative to the separation system (sample, mobile phase and stationary phases). Most columns are constructed of stainless steel for highest pressure resistance. PEEK™ (an engineered plastic) and glass, while less pressure tolerant, may be used when inert surface are required for special chemical or biological applications.

Separation performance Resolution:-

The degree to which two compounds are separated is called chromatographic resolution [RS]. Two principal factors that determine the overall separation power or resolution that can be achieved by an HPLC column are; mechanical separation power, created by the column length, particle size and packed-bed uniformity, and chemical separation power, created by the physiochemical competition for compounds between the packing material and mobile phase. Efficiency is measure of mechanical separation power and while selectivity is a measure of chemical separation power.

Comparison of column of HPLC and UPLC:-

Parameter	HPLC	UPLU
Length	4.6 x 100 mm	2.1 x 100mm
Particle size	5 m	1.7 m
Pressure	1,100 psi	12 psi

Table 2: Comparison of column of HPLC and UPLC

Mechanical separation power-efficiency:-

If a column bed is stable and uniformly packed, its mechanical separation power is determined by the column length and the particle size. Mechanical separation power, also called efficiency, is often measured and compared by a plate number [symbol = N]. Smaller-particle chromatographic beds have higher efficiency and higher backpressure. For a given particle size, more mechanical separation power is gained by increasing column length. However, the trade-offs are longer chromatographic run times, greater solvent consumption, and higher backpressure. Shorter column lengths minimize all these variables but also reduce mechanical separation power.

Chemical separation power-selectivity:-

The choice of combination of particle chemistry [stationary phase] and mobile phase composition-the separation system-will determine the degree of chemical separation power [how we change the speed of each analyte]. Optimizing selectivity is the most powerful means of creating a separation; this may obviate the need for the brute force of the highest possible

mechanical efficiency. To create a separation of any two specified compounds, a scientist may choose among a multiplicity of phase combinations [stationary phase and mobile phase] and retention mechanisms [modes of chromatography].

Effect of column design parameters on efficiency:-

The main difference between the HPLC and UPLC is nothing but only the column parameters from this we can imagine how important the column is. The column is the heart of the chromatographic system; and it is the only device where actual separation of the analyte mixture takes place.

Retention time:-

The distance of the peak maxima from the injection point expressed in time units is called retention time (TR), and it serve as an identifier for the given analyte on that particular system. Retention time is probably the most widely used descriptor of the analyte behavior and it is most easily measurable parameter. However, even though it is easily measurable, it is the least universal parameter. It was found that the retention time in UPLC is less than that of HPLC.

Retention factor:-

The analyte retention consists of two parts:

(1) The time component resides in the mobile phase actually moving through the column, and

(2) The time analyte is retained on the stationary phase.

The difference between the total retention time [TR] and the holdup time is called the reduced retention time [t _ R], and corresponding difference between the analyte retention volume and the void volume is called the reduced retention volume. The ratio of the reduced retention volume to the void volume is widely used dimensionless parameter called retention factor the retention factor of the UPLC is higher than the HPLC.

Figure5:- showing retention time

UPLC presents the possibility to extend and expand the utility of conventional HPLC, a widely used separation science. The ACQUALITY UPLC system is the first instrument of its type to incorporate Intelligent Device Management Technology.

Original HPLC verses optimized UPLC parameters:

Parameters	HPLC Assay	UPLC Assay
Column	Xterra, C18, 50 x 4.6mm, 4 m particles	UPLC BEH C18, 50x 2.1 mm, 1.7 m particles
Flow rate	3.0 ml / min	0.6 ml/ min
Needle wash	Methanol	Methanol
Injection volume	20 L	3 L partial loop fill OR 5L full Loop fill
Gradient (time in min.) ACN:H_2O	T0 (25:75) T6.5 (25:75) T7.5 (95:5) T9 (25:75) T10(25:75)	T0(36:64) T1.1 (95:5) T1.3(36:64)
Total run time	10 min	1.5 min
Total solvent consumption (including 0.5 min of delay time in between injection)	Acetonitrile : 10.5ml, Water:21.0ml	Acetonitrile: 0.53 ml, Water: 0.66 ml
Plate count	2000	7500
USP resolution	3.2	3.4
Lower limit of quantization (LOQ)	~0.2 g/ml	~0.054 g/ml
Delay volume	~720 L	~110 L

Table 4: Original HPLC verses optimized UPLC parameters

Contrasting HPLC and UPLC

• UPLC gives faster results with better resolution

• UPLC uses less of valuable solvents like acetonitrile which lowers cost

• The reduction of solvent use is more environmentally friendly Reference 6 19 ME 330.80: Role of Chromatography & Mass Spectrometry in Biological research http://www.hopkinsmedicine.org/mams/ UPLC columns an ethylene bridged hybrid (BEH) structure

• Superior mechanical strength

• Efficiency

• High pH stability and peak shape for bases

• C8; C18;Phenyl; HILIC

• pH range 1-12

• Max pressure 15,000psi

• Particle size 1.7um • Pore diameter/volume 130A 0.7 mL/g

• Surface Area 185 m^2/g

• Peptides • Proteins

• Oligonucleotides DNA/RNA

• Amino acids

Genetic variation of carotenoids in Chinese bread wheat cultivars and the effect of the 1BL.1RS translocation

ADVANTAGES :

"An ultra-performance liquid chromatography (UPLC) system offers higher sensitivity, faster analysis and better resolution than high performance liquid chromatography (HPLC), and was first developed by the Waters Corporation . Separation in UPLC is performed under very high pressure, and separation efficiency is significantly improved over HPLC [19] . Thus, the objective of the present study was to determine the variation in carotenoid content (including composition and concentrations) among 217 bread wheat cultivars using the UPLC system.

"Characterization of the Principal Constituents of Danning Tablets, a Chinese Formula Consisting of Seven Herbs, by an UPLC-DAD-MS/MS Approach

- "However, ultra-high performance liquid chromatography coupled to diode array detection and mass spectrophotometer (UPLC-DAD-MS) has recently been widely used in this area because can achieve both higher sensitivity and shorter analysis times [11], which is essential for efficient analysis of trace amounts of chemicals. UPLC uses high pressure pumps to accommodate the use of sub-2 µm particle size columns, which can contribute to robust andrapid sample analysis [12]. DAD provides abundant information for structural elucidation of the compounds when it is integrated with tandem mass spectrometry. "

DISADVANTAGES:

A major disadvantage of UPLC is the higher back pressures compared to conventional HPLC which decreases the life of columns. Increasing the column temperature reduces the back pressure problems in UPLC. Moreover, the particles of less than 2 micrometer are most non- regenerable and therefore, have a narrow use.

Applications of UPLC(3)

Determination of Pesticides in Groundwater ;

UPLC coupled with triple quadrupole tandem mass spectrometry (UPLC^{TM}-MS/MS) can be utilized to determine the trace level pesticides in groundwater in less time and speedy manner. The technique has enhanced the analysis speed, sensitivity, and resolution.

Improved Resolving Power in Peptide Maps;

Peptide mapping is an essential technique for the characterization of proteins. Due to exceptionally reduced instrument and column dispersion, the analyzes of tryptic digest of phosphorylase by UPLC technology provides significantly improved resolution, peak capacity, and sensitivity compared to HPLC, allowing the detailed characterization

Rapid Dose Formulation Analysis :

Nowadays, the use of UPLC together with UV and MS detection has been widely utilized in pharmaceutical applications. Several commercial drug formulations were used as models to study the efficiency of separations with the change of flow rate. The efficiency was judged on the parameters of resolution, theoretical plates, column ruggedness, retention time, and peak area. For example, mefenamic acid and chloramphenicol separation was studied in dimethylacetamide/ polyethylene glycol-200 vehicle.

Analysis of Traditional Chinese Medicines (TCM);

The identification and quantification of components of TCM by chromatographic analysis is one of the major challenges. TCM is a complex matrix in which all the constituents play a specific role for the overall efficacy. Therefore, the analysis of all the constituents is synchronously necessary for the quality control. The new technique UPLC is used for the quality control of the TCM.

Multi-Residue Analysis of Pharmaceuticals in Waste Water;

The water used in the pharmaceutical companies is found to have the traces of various cholesterol-lowering statin agents, anti-ulcer agents, antibiotics, beta-blockers, analgesics, anti-inflammatory agents, lipid regulating agents, psychiatric drugs, and histamine H2 receptor antagonists. UPLC coupled with Q-TOF-MS is used to confirm and screen these drugs in the samples of waste water treatment plant.

Identification of Metabolites ;

The identification and detection of all the possible metabolites of the candidate drugs for the discovery of new chemical entities is a very important step. For the identification of the metabolites, a high sample throughput is required to be maintained by the analysts to provide

quick results to the medicinal chemists. UPLC-MS/MS is helpful in biomarker discovery as it meets tough analytical requirements and provides sensitivity, mass accuracy, dynamic range, and resolution.

In Manufacturing / Quality Assurance (QA) / Quality Control (QC) ;

Identification, quantification, purification, efficacy and safety are key parameters to be evaluated during manufacturing of a drug product and pharmaceutical dosage form. Material stability is also observed as a component of QA and QC. UPLC is used as an important tool in QA/QC laboratories for the quantitative and extremely regulated analysis.

Impurity Profiling ;

Efficient for consistent detection and separation of all the impurities present in the active compound. The drug development and formulation process demand accurate measurement/testing of low-level impurities present with the active pharmaceutical ingredients or the excipients or the raw materials used in the preparation of the final product. Thus, the presence of excipients in the sample makes the profiling difficult and with HPLC method, it takes longer time for analysis to achieve sufficient resolution. Thus, the combination of UPLC with mass spectrometry has been useful for the documentation of drug and endogenous metabolites in the final product.

Method Development / Validation ;

Method development and validation is a complex process and consumes a lot of time. For the development of a robust and reliable method, the labs are required to study many combinations of different parameters e.g. mobile phase, temperature, pH, column and gradient chemistry etc. UPLC is an important method used in the laboratory which reduces the cost and increases the efficiency of analysis required for developing and validating the method. With UPLC, the speed of the separation increases and efficiency improves, which results in the fast development of methodologies. High stability of the UPLC columns provides the possibility of selection of column temperature and pH from a wide range.

Forced Degradation Studies (FDS) ;

This study is done to access the chemical stability of the candidate compound in the pharmaceuticals. Usually, it is performed at the preliminary stage in the process of drug development. Forced degradation/ stress testing is performed under accelerated environment. The experimental conditions cause the candidate compound to degrade under extreme conditions like acid and base hydrolysis, peroxide oxidation, photo-oxidation and thermal stability to identify the resultant degradation products. This helps to establish degradation pathways and thus intrinsic stability of a drug substance. The stability of product describes shelf life and storage conditions

and helps in the selection of appropriate formulations and their suitable packaging. This is compulsory for regulatory documentation. The commonly used analytical approach for FDS is HPLC with UV and/ or MS but these techniques consume a lot of time and not provide high resolution to confirm the precise detection of degradation products. Use of UPLC with photodiode array and MS analysis supports the identification of degradation products and also reduces the time needed to evolve stability indicating methods. Fig. (6) is a chromatogram of FDS of glimepiride done on UPLC BEH C_{18} column. It shows the sharp peaks of different degradation products along with glimepiride.

Chromatogram of high resolution analysis of Glimepiride forced degradation on BEH C_{18}.

Dissolution Testing :

Dissolution testing is one of the most important step carried out during formulation and manufacturing process to test the drug release. The dissolution data provides understanding to validate consistency and uniformity of the active ingredient in every batch. Testing of potent drugs in sustained release dosage form is very important as their dissolution studies data can affect the delivery of the medicine. Moreover, new and potent formulations require higher separation sensitivity. UPLC method provides accurate and consistent automated online sample acquirement.

Bioequivalence / Bioanalysis Studies ;

Bioequivalence studies are pharmacokinetic studies needed for the quantitation of drugs in biological samples. This is an important step to compare the rate and exposure level of newly developed formulations of prevailing drugs with that of the original formulation. The selectivity and sensitivity of UPLC-MS/MS produce reliable and precise data. UPLC- MS/MS solutions have increased efficacy, output, and profitability for the bioequivalence laboratories. UPLC sample manager enhances the effectiveness by considering a huge number of samples in a temperature controlled atmosphere, confirming maximum throughput which increases the sensitivity and quality of data acquisition rates of tandem quadrupole MS systems.

Toxicity Studies;

During the drug development process, toxicity issue causes a fall out of drug candidates and this causes monetary loss to the organization. It is a complicated task to estimate candidate drugs for possible inhibition or initiation of metabolizing enzymes, toxicity or drug-drug interactions in the body. UPLC allows precise detection due to its high resolution. Further, its sensitivity also allows the detection of the peaks at low concentrations. These factors lessen the time for analysis and decrease failure of sample analysis.

Iodinated Disinfection Byproducts (IDBPs);

Till date, a few numbers of IDBPs have been characterized in drinking water by using GC/MS. But with the help of coupling UPLC to the electrospray ionization-triple quadrupole mass spectrometer (ESI-tqMS), pictures of IDBPs in samples of water, treated with chlorine and chlorine- ammonia have been collected and 17 IDBPs structures were provisionally projected.

Therapeutic Drug Monitoring ;

Carlier et al in 2012 reported the monitoring of β- lactam antibiotic concentration in plasma of patients with different pharmacokinetics. In their studies, they tried to validate a UPLC-MS/MS method for the simultaneous estimation of two β -lactamase inhibitors and seven β- lactam antibiotics in human plasma. The main benefit of the technique is the faster speed of analysis (5.5 min /sample) compared to other approaches used for this type of multiple analytes.

Analysis of Explosives ;

UPLC proved to be an enhanced procedure to analyze various explosives. In addition, analysis of explosive remains from hand swipes can also be detected by UPLC with minimal sample preparation requirement (less than 9 min), thus enhancing the lab output as well as freeing up valuable MS time for further analysis

Analysis of Contaminants in Foodstuffs ;

Intensive color of Sudan dyes lured frauds for improving the color of several spices and food stuffs which can form DNA adducts causing mutations. UPLC coupled to tandem mass spectrometry allows the identification of Sudan at low ppb levels in spices and chilli containing food stuffs. Fig. (7) shows the chromatogram of Sudan I-IV and it also contains the fast peaks of sudan II, III and IV. These fast peaks are additional peaks as these eluted a few minutes before the main peak of the compounds.

Dendrimers Characterization ;

Dendrimers are highly branched symmetric polymers having a compact round structure (diameter 1.1nm to 9 nm) and unique behavior. They are normally synthesized from a central polyfunctional core by repetitive addition of polymers. Dendrimers surfaces provide a brilliant stage for the attachment and appearance of cell specific targeting groups, solubility modernizers and stalth moieties that decrease immunological interactions. Polyamidoamine (PAMAM) dendrimers are one of the widely used dendrimers. HPLC has been utilized to isolate and to check the purity of many PAMAM dendrimer generation or conjugates. This technique also helps to study the solubility of multi functionalized dendrimers and the interactions between

them and biomolecules. UPLC reduces the retention time of analytes with an improvement of the resolution proficiency during dendrimers studies

Determination of Phytoconstituents;

UPLC can be used to identify and quantify procyanadines, phenolic compounds, monomers, oligomers, isoflavones, flavonoids, coumarins and alkaloids such as caffeine and theobromine. Fig. (8) shows the comparison of chromatograms for analysis of coumarins using HPLC and UPLC methods. It is clear from this figure that UPLC method completes the process in less time and sharp peaks are obtained.

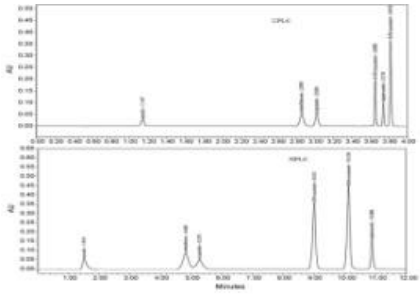

Fig. Chromatogram of the Analysis of Coumarins by HPLC and UPLC.

Identifying Static and Kinetic Lipid Phenotype ;[5]

High resolution UPLC-MS is employed to study the concentration of lipids and their endogenous production. Therefore, this technique was found to be useful in determining the contribution of different pathways and synthesis that could affect lipid biology.

Analysis of Free Amino Acids (FAA) in Wines ;

The production of FAA in the less aged white wines can be determined by the UPLC. The UPLC^{TM} method is an established method for the analysis of amino acids using 6-aminoquinolyl. This new UPLC^{TM} method has made the separations quick and reliable for 24 amino acids within 23 minutes. This method proved to be superior compared to original HPLC method due to much improvement in resolution with reduced run time. Fig. (9) shows the contribution of UPLC in monitoring the complex autolysis processes during the on-lees aging of wines.

Identification of Metabolic Biomarkers to Diagnose Epithelial Ovarian Cancer (EOC);

Currently available tests are insufficient to distinguish patients with EOC from normal individuals. Plasma specimens of EOC patients and normal individuals were analyzed using UPLC/QTOF/MS. Eight biomarkers were identified which may serve as novel biomarkers for diagnosis. Fig. (10) shows the application of UPLC in the diagnosis of EOC.

ADME

ADME studies include absorption, digestion, metabolism, and elimination. Yan developed and validated the sensitive UPLC-MS/MS method for the pharmacokinetic studies of HZ08 liposome injection in plasma and tissues of rats to study plasma kinetic and tissue distribution respectively.

Drug Abuse

UPLC-MS/MS method can be used to develop and evaluate a fast, robust and specific screening platform for the determination and quantification of a variety of commonly used drugs of abuse (opioids, benzodiazepines etc) in urine.

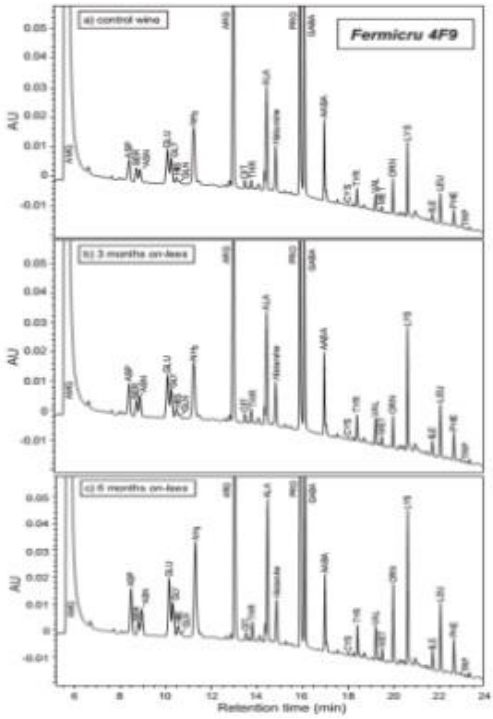

Fig. UPLC™ chromatograms of FAA profiles for the wine set fermented with the yeast Fermicru 4F9, (a) control wine, (b) 3 months, and (c) 6 months on-lees maturation.

CONCLUSION

UPLC is one of the most important tools in analytical chemistry which increases the speed, resolution, and sensitivity of the chromatographic analysis and decreases the time, solvent consumption and cost involved. The peaks obtained through UPLC have decreased noise and better signal to noise ratio. It gives sharp and narrow peaks of more or less all categories of pharmaceutical drugs. It also facilitates the analysis of complex mixtures in less time and the peaks obtained through this method depicts more information which is more clearer in comparison to the peak obtained through HPLC. This method is widely used for the analysis of different pharmaceuticals such as amino acids, peptide mapping, glycans analysis, phenotyping,

drug discovery, metabolomics etc. This technology thus creates a new opportunity for business profitability in highly efficient manner and allows the product to be introduced to the market in less time.

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