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UPLC: A PREEMINENT PHARMACEUTICAL ANALYSIS TECHNIQUE

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Abstract: Today's pharmaceutical businesses are motivated to develop new and more effective methods for medication discovery, development, delivery, and monitoring. The creation of a quick chromatographic process is essential for analytical labs in this competition. Significant technological advancements have been made in the last ten years in the areas of particle chemistry performance, detector design, system optimization, data processing, and other chromatographic method controls. Ultra-high performance liquid chromatography (UPLC), which holds back the premise of HPLC technique, produced exceptional performance when all was combined. By utilizing particles smaller than 2 µm and operating at higher pressure, UPLC exhibits a significant improvement in speed, resolution, and sensitivity of analysis, and the mobile phase may be able to run at higher linear velocities than HPLC. In the field of liquid chromatographic investigations, this approach is regarded as a new focal point. The fundamental principles, equipment, and benefits of UPLC over HPLC are the main topics of this review. Additionally, this article highlights the numerous pharmaceutical uses of this method.

Keywords: Liquid chromatography, ultra-high performance liquid chromatography, and ultra-high performance liquid chromatography-mass spectroscopy

A significant shift has occurred since the advent of ultra-high performance liquid chromatography (UPLC), which allows analysts to acquire quick analytical separation procedures without compromising the high-quality results previously obtained by high performance liquid chromatography (HPLC). UPLC will eventually replace all of the traditional HPLC methods, according to many laboratory professionals (1). The primary drawback of the immaculate separation method of HPLC is its low efficiency when compared to gas chromatography or capillary electrophoresis, despite its many benefits, including robustness, ease of use, and adjustable sensitivity and selectivity (2, 3). The fundamental idea behind UPLC, a variant of HPLC, is that efficiency and resolution rise as column packing particle size decreases. According to the standard Van Deemter equation (4), efficiency increases significantly when particle size is reduced to less than 2 □m and does not decline at higher linear velocities or flow rates. The speed of analysis and peak capacity, or the number of peaks resolved in a given amount of time, can be

extended to their maximum values by utilizing the smaller particles, and these results are far superior than those previously attained by HPLC. Additionally, the following actions must be taken in order to increase efficiency:

1. Elevated temperature range should be employed, which will allow high flow rate of mobile phase by reducing its viscosity and thus it will signifi- cantly reduce back pressure (5ñ9).
2. Monolithic columns should be used, which con- sist of one piece of solid that possesses intercon- nected skeletons and interconnected flow paths (through-pores). Earlier, monolithic columns were introduced exclusively for organic-poly- mer-based materials (10ñ12) including com- pressed soft gels, while short columns (about 1 mm; monolithic disks) were introduced for rapid separation of proteins.

These columns have poly- merized porous support structure that provides lower flow resistance than conventional particle- packed columns (13ñ18).
UPLC is a technique which comprizes the above mentioned features and stands better than HPLC in many ways as it shows better chromato- graphic resolution, performs more sensitive analy- sis, consumes less time, reduces solvent consump- tion (19ñ23) and has high analysis speed (24ñ26).

Contribution of small particles in UPLC

The small particle size (i.e., less than 2 µm) of stationary phase is the basis of UPLC technique. The basal principle of this technique is governed by an empirical formula known as Van Deemter equa- tion (27) that describes the relationship between lin- ear velocity (flow rate) and plate height (HETP or column efficiency). This equation shows that enhancement of efficiency of UPLC technique can- not be accomplished without using smaller particle size than those used in conventional HPLC tech- nique. In Figure 1, Van Deemter plot demonstrates that as the particle size decreases less than 2 □m there is a significant gain in the efficiency, and this condition is well maintained even if there is an increase in flow rate or linear velocities. This plot indicates that the usable flow range which shows good efficiency is much greater for smaller particles as compared to the larger particles (28, 29). The Van Deemter plot is governed by the equation: $H = A + B/v + Cv$, where v is linear velocity and A, B and C are constants. A is independent of velocity and rep- resents the ìEddy" mixing and when column parti- cles are uniformly small, the value of A is the low- est. B is axial diffusion or the natural diffusion ten- dency of molecules and this effect is diminished at high flow rates, so this term is divided by v. C is due to kinetic resistance to equilibrium in the separation process. The design and development of required 1.7 µm particles was a challenging task, on the con- trary, researchers have shown keen interest in the development of these particles in order to capitalize their advantages. Despite, the availability of high efficiency non porous 1.5 µm particles in the market; they were not employed in UPLC columns due to their poor loading capacity and retention due to low surface area. UPLC required porous particles, which can withstand the high pressure in order to maintain their retention and capacity similar to that of HPLC (30, 31). Silica particles possess good mechanical strength but their application was limited by narrow pH application

range and generally exhibit tailing during analysis of basic analytes (32). However, polymeric columns did not have any pH limitations but found to have low efficiency. In 2000, the first generation hybrid chemistry utilizes the classical sol-gel synthesis method to create durable columns that incorporated carbon in the form of methyl groups (33, 34). These columns exhibit several advantages such as mechanical strength, high effi- ciency and are operative over an extended pH range. However, they do not possess enough mechanical stability necessitated by UPLC. Consequently, the second generation bridged ethane hybrid (BEH) technology was developed (35ñ37). This technology increases the mechanical stability of 1.7 µm parti- cles by bridging the methyl groups in the silica matrix as shown in Figure 2 that lead to the produc- tion of the columns which can withstand high pres- sure and pH. These BEH columns are highly effi- cient as efficiency of a column is directly propor- tional to its length and is inversely proportional to the particle size. The application of BEH columns resulted in the detection of additional drug metabo- lites, superior separation and improved spectral quality (38, 39).

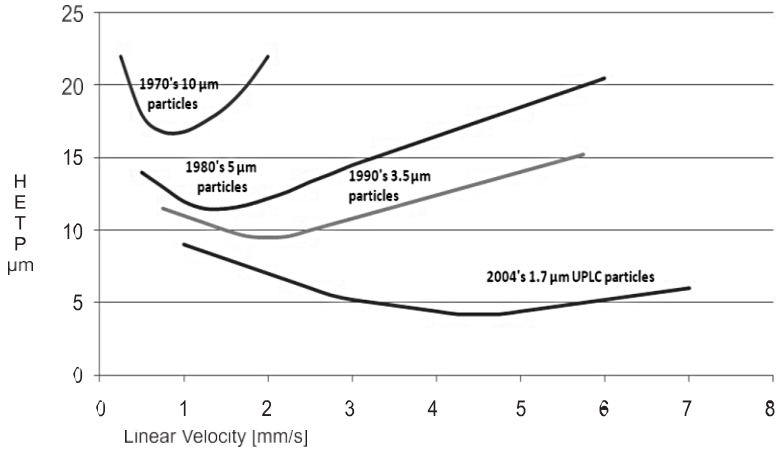

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Figure 1.Van Deemter plot illustrating the evolution of particle sizes over the last three decades

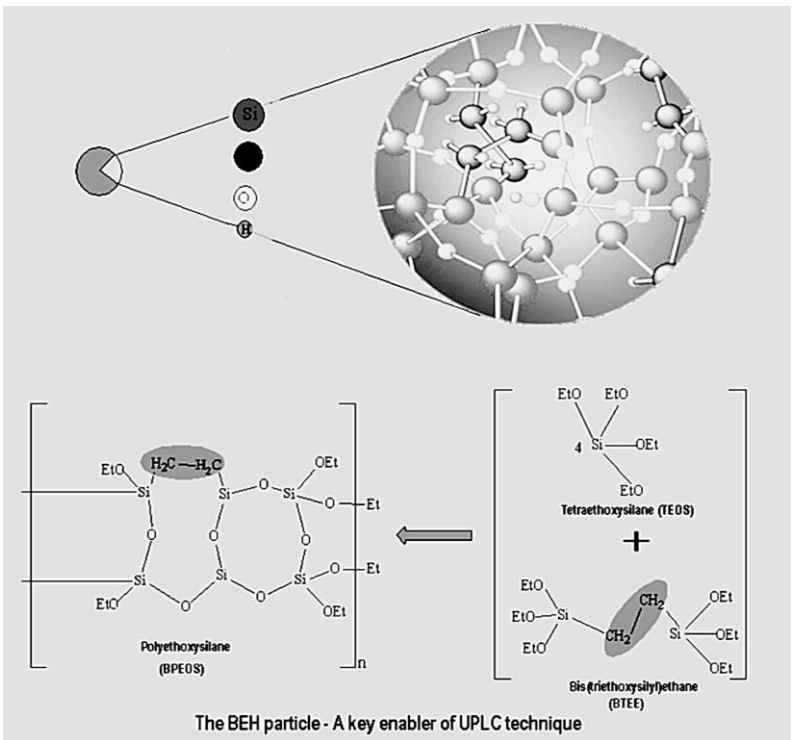


Figure 2. Synthesis of 1.7 µm particles for UPLC by BEH technology

INSTRUMENTATION

The basic instrument in UPLC technique had to keep its tempo up in order to take advantage of the enhanced speed, superior resolution and greater sen- sitivity provided by small particles. A design with advanced technology in the pump, autosampler, detector, data system, and service diagnostics was required to fulfil the purpose. The basic instrumen- tation of UPLC is discussed below.

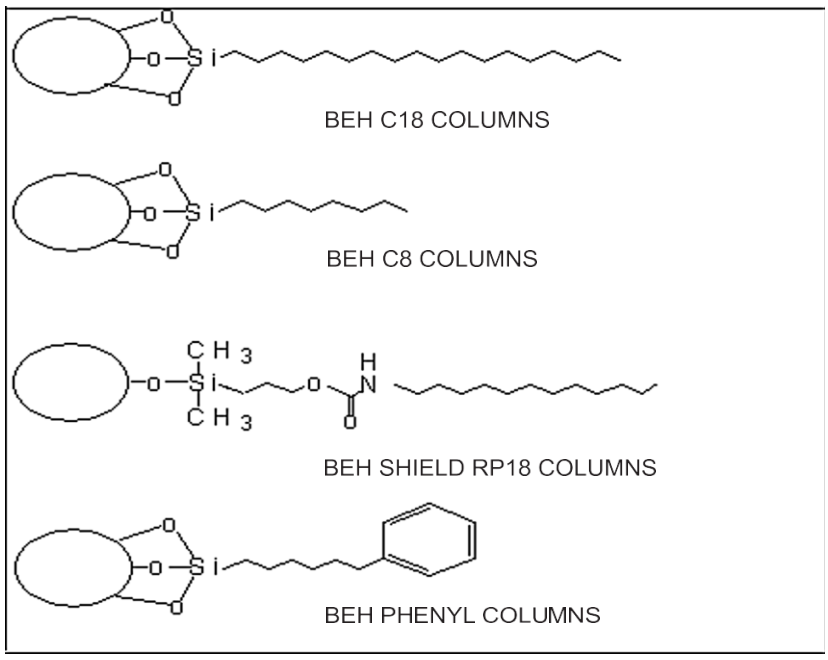
Pumping devices

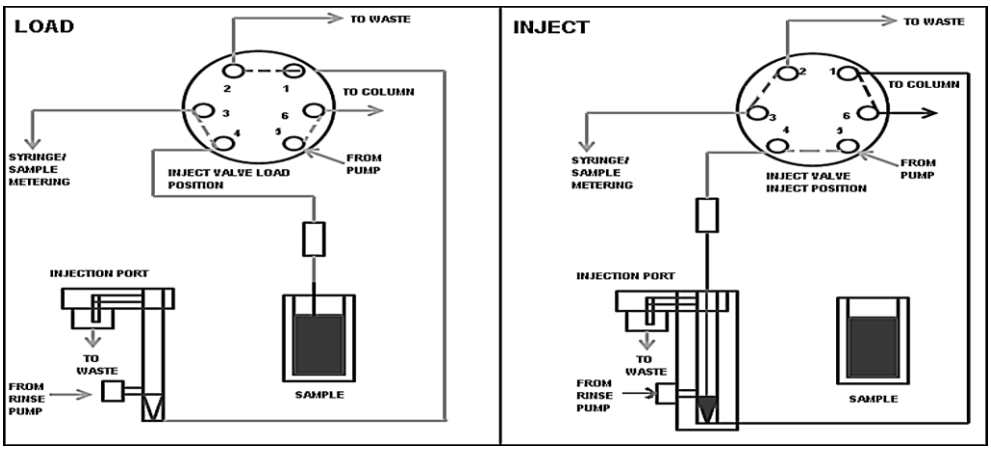
An ideal pump for UPLC has a capacity of delivering solvent at higher pressure around 15000 psi for the optimum flow rate with maximum efficiency across 15 cm long column packed with 1.7 µm particles (40, 41). UPLC uses two serial pumps with pressure limit of 1000 bar (42, 43) and have inbuilt solvent selector valves, which have the capa- bility to choose the accurate solvent ratio from up to four solvents (44).

Sample injector manager

The UPLC system with its flow through-needle design sample manager addresses three design chal- lenges for reliable performance: robust sealing of the needle at higher pressure, minimizing the extra- column band spread for narrow peaks and perform- ing pulse free injection process to protect column from extreme pressure fluctuations. When an injection is initiated, the inject valve diverts flow from the needle in order to collect sample from the vial as shown in Figure 3. The needle is inserted into the vial to withdraw the exact volume of the sample required and then it returns to the injection port. The needle is pushed against the internal sealing surface of the port and the injection valve turns and the sam- ple is pushed down to the injection port.

Figure 3.The injection sequences of UPLC in both load





and inject phase

Figure 4. UPLC column chemistries

Dispersion of the sample can be minimized by keeping less dis- tance between the injection port and the inject valve. After injecting the sample, the needle is washed for a specified amount of time to minimize sample car- ryover. Beside this, there are also direct injections for biological substances mentioned in the literature (45, 46).

Table 1. Account of drug components separated by using UPLC technique

No.	Components analyzed	Column specifications	Mobile phase flow rate (mL/min)	Retention time (min)
1.	Metoprolol (MT), Atorvastatin (AT) and Ramipril (RM) from capsules dosage forms (49)	ZorbaxÆ XDB-C18 (4.6 ◊ 50) mm,	1.0	1.3, 2.1 and 2.6 for MT, AT and RM, respectively
2.	Aspirin (ASP), Clopidogrel bisulfate (CLP) and Atorvastatin calcium (ATV) from capsule dosage form (50)	Acquity BEH C18 column (2.1 ◊ 50 mm, 1.7 µm)	0.35	0.59, 1.04 and 2.89 for ASP, CLP and ATV, respectively
3.	Fexofenadine in human plasma with carbamazepine as internal standard (51)	Acquity BEH C18 column (2.1 ◊ 100 mm, 1.7 µm)	0.25	9.58 and 4.69 for fexofenadine and carbama-zepine, respectively
4.	Secnidazole (SNZ), Fluconazole (FCZ) and Azithromycin (AZTM) in tablet dosage forms (52)	Acquity BEH Shield RP18 column (2.1 ◊ 100 mm, 1.7 µm)	0.3	3.7, 4.1 and 6.2 for SNZ, FCZ and AZTM, respectively
5.	Narirutin, Hesperidin, Naringin, Neohesperidin and Meranzin hydrate in *Fructus aurantii*-type preparations (53)	Acquity BEH C18 column (2.1 ◊ 100 mm, 1.7 µm)	0.3	6.8, 8, 9, 10.1 and 11.6 for narirutin, hesperidin, naringin, neohesperidin, meranzin hydrate, respectively
6.	Diclofenac (54)	Acquity BEH C18 column (2.1 ◊ 50 mm, 1.7 µm)	0.6	1.5
7.	Fourteen different samples of Rheum palmatum L (55)	Acquity BEH C18 column (2.1 ◊ 50 mm, 1.7 µm)	0.4	In between 0ñ10 for all 14 samples

8.	Catechin, epicatechin, B2 and B5 (epicatechin-4a-8-epicatechin), C1 and tetramer D (epicatechin-4a-8-epicatechin-4a-8-epicatechin) in chocolates (56)	Acquity BEH C18 column (2.1 ◊ 50 mm, 1.7 µm)	0.3	In between 0ñ3 for all six compound
9.	Hippurylñhistidylñleucine (HLL) and hippuric acid (HA) for assaying angiotensin converting enzyme activity (57)	Acquity BEH C18	0.4	1.12 and 1.37 for HA and HHL, respectively
10.	Seven steroids; dienogest, finasteride, gestodene, levonorgestrel, estradiol, ethinylestradiol and norethisterone acetate (58)	Acquity BEH C18 column (2.1 ◊ 50 mm, 1.7 µm)	0.55	Less than 2.5 for all seven steroids
11.	Aspirin (AP) and Dipyridamole (59)	Hypersil Gold C18, column (1.9 µm, 100 mm ◊ 2.1 mm)	0.5	0.83 and 1.62 for AP and DL respectively.
12.	Raloxifene hydrochloride and its related impurities (60)	Extended C18, 50 mm ◊ 3.0 mm ID with 1.8 microns particles.	0.7	Retention time of different impurities was 0.70, 1.59, 2.46 and 6.05.

Columns

The UPLC columns are made up of small par- ticles having size less than 2 µm. The role played by small particle size in UPLC technique has been mentioned above. The particles are bonded in matrix as the bonded stationary phase is required for pro- viding both retention and selectivity. Four bonded stationary phase (Fig. 4) columns manufactured by ACQUITY are available in the market, which can be used by UPLC technique (47, 48).

- BEH C18 and C8 columns ñ These are straight alkyl chain, most preferred UPLC columns as they can be used over wide pH range. The tri- functional ligands produce low pH stability, which is combined with high pH stability of 1.7 µm BEH particles to produce the widest usable pH operating range.
- BEH Shield R18 columns ñ They provides selec- tivity to UPLC as it complements C18 and C8 columns.
- BEH Phenyl columns ñ They has tri-functional C6 alkyl ethyl between the phenyl rings and the silyl functionality.
- BEH Amide columns ñ The combination of tri- functionally bonded amide phase with BEH small particles provides exceptional column life time. They facilitate the use of a wide range of phase pH i.e., from pH 2 to 11.

Detectors

Two tuneable UV-visible photodiode array detectors namely ACQUITY PDA and ACQUITY PDA e□ detectors are generally used for the routine analysis and method development, which have the power of detecting and quantifying trace impurities. The data rates of these detectors are up to 80 Hz hav- ing low noise specification i.e., 10 Au with wide range of spectra analysis up to 500 nm (PDA detec- tor) and 800 nm (e□ detector). To avoid band spreading and concentration variance, low volume light guiding flow cells are used comprising of Teflon AF, which eliminates the internal absorption by using total internal reflection principle to enhance the light transmission efficiency.

Applications

This technique has been successfully applied to pharmaceutical analysis of numerous drugs, a few of them are enlisted in Table 1 (49ñ60), with the improvement in the factors like retention time and mobile phase consumption. Narasimham and Barhate developed and validated UPLC method for the simultaneous determination of □-blockers and diuretic drugs in pharmaceutical formulations with the objective of reducing analysis time and main- taining good efficiency (61). The chromatographic separations of all the drugs were achieved on a Waters Acquity BEH C18, 50◊2.1 mm, 1.7 □m UPLC column within a short runtime of 2.6 min. The results obtained were compared with the previ- ously developed HPLC methods (Table 2). The elu- tion time of all the drug compounds in UPLC were observed to be reduced by 10-fold. The higher peak capacity, i.e., 1494 in UPLC as against in HPLC i.e., 942, conforms the better gradient separation effi- ciency and resolving power of UPLC system. Furthermore, the applications of this technique are discussed below:

Rapid analysis of products

Before the introduction of this technique, chro- matographers were compromising with the factors like low speed and resolution .Even in the case of natural products more resolution was required to get apt knowledge of the additional peaks. UPLC can be extensively used in the analysis of natural products and herbal medicines.

In 2004, the first commercial- ly available UPLC system was the ACQUITY UPLC that fulfilled all the requirements needed for the separation of various pharmaceutical products related small organic molecules, proteins and pep- tides (62).

Table2. Comparison of system performance of HPLC and UPLC.

Drug component	Retention time		Capacity factor		USP tailing		Resolution		Peak capacity	
	HPLC	UPLC	HPLC	UPLC	HPLC	UPLC	HPLC	UPLC	HPLC	UPLC
Metoprolol	13.4	1.9	4.3	8.9	1.4	1.2	2.7	26.9	942	1494
Amiloride	10.2	1.1	3.1	4.7	1.1	1.2	–	–		
Hydrochlorothiazide	12.8	1.3	4.1	5.4	1	1.1	13.9	5		
Amlodipine	17.6	2.2	6	10.4	1.2	1.6	6.8	4.4		
Propranolol	16.4	2.1	5.6	9.8	1.2	1.3	15.5	6.4		
Felodipine	24.3	2.6	8.7	11.9	0.9	1.5	41.2	2.9		

Table 3. Comparative study of parameters used in HPLC and UPLC technique.

No.	PARAMETER	HPLC	UPLC	INFERENCE
1	Particle size	3ñ5 µm	Less than 2 µm	Reduction in analysis time
2	Mobile phase flow rate	More	Less	Lesser mobile phase consumption
3	Injection volume	5 µL (Std. in 100% methanol)	2 µL (Std. in 100% methanol)	Can deal with even small traces of sample
4	Column	ALLTIMA C18, ZORBAX C8	ACQUITY UPLC BEH C18 and C8	Can withstand high pressures and have high mechanical stability and efficiency
5	Column dimension	150 ◊ 3.2 mm	150 ◊ 2.1 mm	Higher resolution
6	Column temperature	30°C	65°C	Increased selectivity, lower solvent viscosity and increase mass transfer rate
7	Maximum back pressure	35ñ40 MPa	103.5 MPa	Faster separation

Identification of metabolites

When a new chemical entity (NCE) reaches the development stage, identification of its metabolites becomes a perpetual process. The detection of all circulating metabolites of a candidate drug is neces- sary. The identification of major metabolites is done by performing *in vitro* discovery studies. The weak spots of metabolites of drug candidate molecules are recognized and hence protected by altering the com- pound structure. Plumb et al. have explored the application of UPLC-MS for analysis of metabolites of candidate drug (63, 64). They also examined the application of UPLC-MS in profiling metabolic pathways for functional genomics studies (65). Their studies revealed that higher resolution of UPLC in terms of specificity and spectral quality diminishes the risk of missing any detection of potentially important metabolites.

Bioequivalence studies

The detection of drug in biological sample is very important to study the pharmacokinetics, toxi- city and bioequivalence of drug. Blood, plasma and urine can be used as biological matrices which con- sist of sample drug in them (66). Previously LC-MS was used for detecting drug in these biological matrices. But nowadays UPLC-MS is used as it has some advantages over LC-MS such as:

- UPLC-MS provides unprecedented performance and compliance support.It has excellent chromatographic resolution and sensitivity. UPLC can accommodate more number of sam- ples than HPLC so sample throughput is enhanced.
- It gives not only high quality results but also ensures the safety of data by using security based data collection software.
- Tolley et al. (67) in their studies have concluded that higher efficiency, better resolution and high- er peak capacity provided by UPLC technique is particularly important for the analysis of proteins and peptides.

Detection of impurities

The detection of impurities in raw material as well as in final product is the most vital phase of the drug development process. Earlier studies have accounted for excellent detection of impurities by HPLC as it has sufficient resolution for the determi- nation of the lowest level of impurities with good reproducibility results, but due to the presence of excipients, there is prolonged HPLC analysis so it becomes necessary to perform several analytical runs to get the required data. This curb can be over- come by using UPLC technique as it offers exact required data and is operational at alternate low and high collision energies. The fast change of collision energy produces both precursor and product ions of all analytes present in the sample, which allows rapid identification and profiling of impurities. Lippert et al. (68) pointed that in some cases, the impurity and compound are of the same molecular weight and have similar structures so they could not be differentiated by MS or LC/MS necessitating higher chromatographic resolution which can be provided by UPLC.

Dissolution testing

Dissolution testing is very important to control the quality and release of drug. In sustained release dosage formulations dissolution is the rate limiting step so this becomes very important in such cases. The dissolution profile of a drug signifies reliability and batch to batch uniformity of API (Active Pharmaceutical Ingredients) in the formulations. Nowadays, newer and relatively high potent formu- lations are coming in the market which requires enhanced analytical sensitivity. This can be fulfilled by UPLC which provides online sample acquisition. By using UPLC, dissolution testing can be fully automated as it can perform functions like data acquisition, analysis of samples aliquots, manage- ment of test results and distribution.

Besides the above mentioned applications, there are some conditions in which UPLC can be applied successfully, few of them are enlisted below:

- Identification and authentication of purity of newly synthesized pharmaceutical compound for which chemists need to be sure that they have synthesized the expected compound. The throughput of UPLC systemís remote status mon- itoring software along with the fast scanning MS allows the chemist to obtain high quality compre- hensive data regarding the candidate compound in the shortest possible time.
- In performing the forced degradation studies or stress testing which are carried out under extreme conditions like peroxide oxidation, acid and base hydrolysis, photo- stability etc. The speed, resolution, and sensitivity of UPLC sepa- rations, when combined with the high-speed scan rates of UPLC-specific photodiode array and MS detection, makes the identification of degradation products more effective and time required to develop stability-indicating method is shortened.
- In performing highly accurate and well regulated, quantitative analyses performed in QA and QC laboratories in pharmaceutical industries.

UPLC ñ a real hope or just hype

UPLC brought new opportunities in pharma- ceutical industries to get rapid analytical separation results while retaining method accuracy and resolu- tion quality. Some laboratory experts believe that this technique will eventually replace all the con- ventional HPLC methods and consider it as a HOPE, while some critics says that UPLC cannot deliver long term and cost effective benefits and termed UPLC as a HYPE. This point of contradiction can be well elucidated by comparing the merits and demerits of the UPLC.

Merits

- There is a fivefold decrease in the analysis time for many separations in comparison to analysis time taken by other chromatographic techniques (69).
- Consumption of solvent is very low as run time is reduced in UPLC.
- Resolution and sensitivity of UPLC is greater than those of other conventional techniques.
- Sample output is enhanced so manufactures can produce more products according to required specification and hence there is reduction in fail- ure of batches.
- Overall operation cost is reduced.
- Scope of multi residue methods is enhanced.
- Some parameters of UPLC which differ from HPLC and will turn in favor of chromatographic techniques are enlisted in Table 3.

Demerits

- UPLC operates at ultra high pressure up to 1000 bars so column requires more maintenance and life of column is reduced (70).
- Phases 1.7 µm sized are non regenerable and thus have limited use.

UPLC has better column technology, which can work under extremely high pressure conditions, have faster rate of detection and moreover, is based on already established HPLC technique so there is a hope that UPLC will increase the quality of pharma- ceutical analyses and productivity of research scien- tists. While it may take some years for UPLC to become full time analytical technique, we remain optimistic that this technique will live up to expectations.

CONCLUSION

When many scientists began to encounter separation problems with the conventional HPLC technique, UPLC, which is based on the much-proven technology of HPLC technique, not only improved but also flourished its usefulness. Due to its superior speed, resolution, and sensitivity, UPLC provides significantly more information per unit of effort than HPLC. Additionally, UPLC uses less solvent and analysis time than all other chromatographic techniques. In contrast, UPLC has characteristics with HPLC, including as resolution, tailing factors, and reproducibility of peak area/peak retention duration. Therefore, in the pharmaceutical sector, transferring an existing HPLC method to a new UHPLC method is both desirable and profitable, as the literature has successfully shown (71, 72). The aforementioned data extraction has shown that UPLC will be a vital and important instrument for improving both the productivity of research professionals and the quality of pharmaceutical analysis.

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