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Review Article

# A REVIEW ON CORE SHELL TECHNOLOGY IN HIGH PERFORMANCE LIQUID CHROMATOGRAPHY: DRUG ANALYSIS

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## *ABSTRACT*

*Column is the heart of the chromatographic systems. Now a days in order to increase the separation efficiency a new technology of column packed with core shell particles was used in HPLC .The core shell particles revolutionized the chromatography industry by providing faster methods without sacrificing resolution .this specialized particles provides higher efficiency and through put which leads to a reduction in solvent consumption. The literature here by describe the performance difference between the core shell particles column and traditional HPLC columns and the results shows that core shell columns are a promising toll in drug analysis.*

***KEYWORDS:*** *Core Shell, HPLC, Column and Separation Efficiency.*

## INTRODUCTION

### 1. Core shell technology:

Among different types of chromatography, high performance liquid chromatography (HPLC) has been most widely used as an essential analysis tool for research, manufacturing, clinical tests, and diagnostics. This is due to its universal applicability and remarkable assay precision [1]. The column is the heart of chromatographic system, common secret among all chromatographers. The challenges in HPLC are highly efficient and fast separation with high resolution and ideally low back pressure for various types of samples, e.g., in pharmaceuticals, food, life science, environmental and also the daily analysis in research labs. In general there are two types of columns, i.e., packed column and monolithic column, have been used as stationary phases for routine HPLC. Silica microspheres are the mostly used packing materials for packed columns. While for monolithic columns, both porous silica and cross linked polymers are frequently used [2]. Porous monoliths containing highly interconnected pores are widely used as monolithic columns for fast separation with low back pressure [3, 4]. The large pores are in the category of macro-pores (>50 nm, around 1m for polymer monolith). For silica monoliths, in addition to the macrospores, mesopores (2–50 nm) are present in the silica wall. The highly interconnected porosity results into high permeability and hence low back pressure even at high flow rates. Satisfying performance has been achieved particularly for large biomolecules [5, 6]. The main obstacles for the wider use of monolithic columns are the reproducibility of the pore structures and the delicate cladding procedure to fit the monolith into a column. As a result, the analysis performance of monolithic columns may varies from batch to batch. Furthermore, the mechanical stability is generally weak for monolithic columns. There is an additional issue with polymer monoliths, i.e., the potential swelling problems in the presence of solvents. Packed columns with silica microspheres are still dominating the market and most widely used. Although various polymer and ceramic microspheres have been used as packing materials, silica microspheres are the mostly investigated and used materials. Both nonporous and porous silica microspheres have been used. For small nonporous particles, the separation occurs on the particle surface and band-broadening is alleviated because of the short diffusion path, thus allowing faster mass transfer [7]. However, due to the low surface area, retention, selectivity and therefore resolution are limited. The loading capacity is also a critical issue. For porous silica microspheres, in addition to the particle surface, the pore surface provides more sites to interact with analyte. For liquid phase separation, the pore sizes are required to be greater than 7 nm to allow sufficient mass transport. For separation of large biomolecules, large pores up to 100 nm may be required for efficient separation [4]. The size of silica particles and the packing quality can significantly affect the performance of the packed columns. Mono disperses silica particles with smaller diameters are employed to achieve high performance separation. However, coming with the use of smaller particles is the considerably increased back pressure [8]. Half of the particle size may double the separation performance (in terms of theoretical plate numbers) but can also quadruple the back pressure at the same time [4]. Micro-spheres are currently the state-of-art on the market for porous silica microspheres. To achieve fast separation on silica microspheres of certain size, a straightforward approach is to increase the flow rate and therefore the pressure drop across the column. Ultrahigh pressure liquid chromatography is thus developed and used. This technique places much stricter requirement on the pumping system and the whole flow system due to the very high operation pressure. In recent years, core–shell silica particles (solid core and porous shell or superficially porous) have been increasingly used for highly efficient separation with fast flow rate and relatively low back pres-sure [9]. The solid core plus the porous shell gives a larger particle and thus low operating back pressure while the porous shell and small solid core can provide higher surface area for the separation to occur. [10]. The advantage with the core–shell particles as packing materials is that the smaller pore volume reduces the volume present for broadening from longitudinal diffusion (B term in the van Demeter equation). The short diffusion path length can reduce the contribution of the C term due to the fast mass transfer [8, 11]. Particle characteristics such as particle size and porous shell thickness can significantly influence separation parameters [12]. As the thickness of the porous shell decreases, the faster mass transfer can lead to improved column efficiency and fast elution time [13, 14]. For chromatographic

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applications, the core–shell silica particles are also widely known as fused-core, solid core or superficially porous particle.

**2. Preparation method for core shell particles:**

In order to create a core-shell particle, sol-gel processing techniques are employed initially. These sol-gel processing techniques incorporate nano-structuring technology, resulting in the growth of a homogenous porous shell, which envelops a compact, non-porous silica core. Core shell particles are less porous than fully porous particles, which leads to lower levels of band broadening and increased rates of efficiency.

Compared to classical fully porous silica materials, *core* shell particles (Figure 1) consist of a solid *core* and a porous shell. Typical 2.6 µm or 2.7 µm or smaller eg 1.7 µm diameter particles enable high speed and high resolution separations keeping the resulting backpressure low enough so that no special and highly sophisticated instrumentation is necessary. The unique mass transfer characteristics of such columns are the ones to "blaim" for not asking for Ultra high performance systems. The father of the technique is Dr. Jack Kirkland, who is considered to be one of the "founders" of HPLC [15].

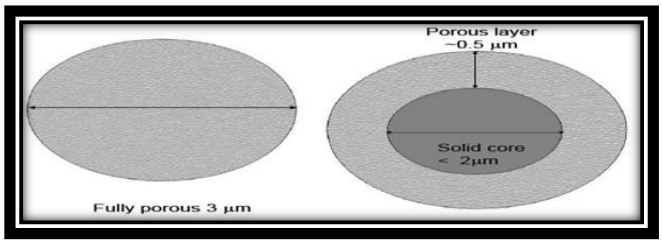


**Fig. 1: Fully porous and core shell particle**

This state of the art technology is also known as solid *core* particles or Fused-*core* particles or superficially-porous, or semi-porous, or pellicular, all referring to similar stationary phases.

Some of the commercially available solid *core* columns are Kinetex™ *core-shell* by Phenomenex, BlueShell® by Knauer, Accucore™ by Thermo Scientific, CAPCELL CORE by Shiseido, HALO™ (fused-core) from Advanced materials technology inc. Ascentis® Express by Sigma-Aldrich and many others [16].

**3. The fundamentals principles of core shell particles for HPLC:**

Comparative studies are performed to investigate the relation between different types of core–shell particles and the column performance. Columns packed with core–shell particles provided high efficiencies with reduced plate height in the range of 1.7–1.5, depending on the test mixtures [17, 18].

The unique core-shell morphology has some very significant advantages in chromatographic performance over fully porous particles, specifically increasing column efficiency and reducing retention time.

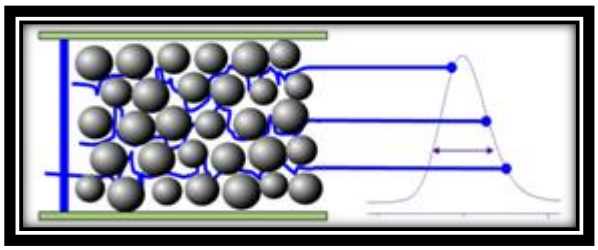

**Fig. 2: Analyte movement in the porous column.**

It shows how an analyte moves through a column with fully porous particles. Unwanted widening of peaks is caused by the wide particle size distribution and slow movement of the analytes into and out of fully porous particle leading to eddy dispersion

If you look at Figure 3 below, you'll see how an analyte moves through a column with core-shell particles. On a column packed with Kinetex core-shell particles, the sample bands travelling through the column exhibit significantly less band broadening during the run from the reduced diffusion path. As a result, the peaks are eluted as much narrower bands, resulting in increased peak height and resolution.

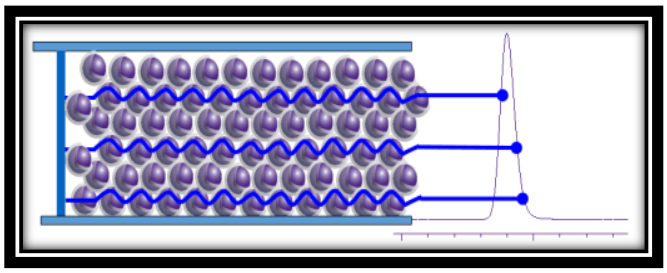

**Fig. 3: Analyte movement in the core shell column**

Increased resolution and peak capacity; the core shell particle decreased band broadening, making the peaks narrower .therefore, an increase in resolution and peak capacity is seen.

Higher sensitivity; again, the reduction in band broadening leads to a higher sensitivity, allowing chromatographers to see lower detection limits.

Using 5µm core-shell particles will result in the efficiency, resolution, and sensitivity of a 3µm fully porous particle. Also, for those with only an HPLC system and needing UHPLC performance, the 2.6µm core-shell particle is a hybrid particle that can straddle the HPLC and UHPLC worlds. This 2.6µm core-shell particle will provide the performance of a sub-2µm fully porous particle. The resulting shortened run time will increase productivity and save time and money.

To fully take advantage of the hybrid 2.6µm particle, the HPLC system needs to be optimized for the lowest dwell volume delivered to the column. Otherwise, the extra column will lead to band broadening and lower efficiency through peak dispersion before and after the column. The fraction of time that an analyte spends inside the HPLC column during a run is productive: analytes are being separated with high efficiency.

**4. Steps that should be taken to optimize the HPLC system include the following:**

1. Use a lower volume needle seat.
2. Use a low volume injection loop.
3. Column switching valves are a great method development tool that adds significant volume to the system. Therefore, bypass the switching valve.
4. Use zero volume finger-tight fittings.
5. Most HPLC systems come with 0.010in ID tubing which has a solvent volume of 1.3µL/inch adding to a significant amount of dead volume. Use 0.005in ID tubing which only adds 0.3µL/inch in volume.
6. The volume after the column is also important and using a lower volume UV flow cell will show a difference in chromatography.
7. Increase detector sampling rate to 20Hz (typically set at 5Hz).
8. A slow detector time constant is normally set to filter out high frequency noise. Unfortunately, this noise filtering can also filter out the sharp peaks and high resolution that core-shell columns deliver. Therefore, increase the detector time constant.

In general, the core-shell particle revolutionized the chromatography industry by providing faster methods without sacrificing resolution. This specialized particle provides higher efficiency and throughput which leads to a reduction in solvent consumption. And finally, the higher sensitivity allows chromatographers to obtain lower levels of detection without using higher amounts of sample.

**5. Applications of core shell particles in drug analysis:**

Destefano et al. reported fast and high resolution separation of naphthalene, virginiamycin, pesticides, and explosives on Halo C18 and C8 columns [18]. The reduced plate height plots for virginiamycin obtained from both columns was significantly lower than 3mm totally porous particles due to increased mass transfer. Guiochon et al. and others worked with the same type of columns, showing improved separation of large molecules such as proteins, moderate molecular

weight peptides, and proteins digests of insulin, lysozyme, myoglobin, and bovineserum albumin [19-22]. Comparing the efficiency of KinetexC18 with Halo C18, it was reported that Kinetex C18 resulted in better performance with no loss in peak capacity with increasing velocity [23]. It was believed that C term in the HETP plot for the Halo particles was significantly larger, which contradicted with the reduced diffusion distance when using reduced velocities. Another study indicated that this increase in performance could be a result of the difference in particles size between the Kinetex (2.6m) and Halo (2.7m) [22]. The result confirmed the very flat HETP curve, the very low C term of the Kinetex column and its ability to successfully operate at high flow rates while experiencing less efficiency loss than other columns [22]. A systematic evaluation was carried out by Oláh et al. to compare the kinetic performance on Kinetex and Ascentis Express (Sigma–Aldrich) columns by constructing the van Deemter, Knoxand Kinetic plots using test mixture of estradiol, levonorgestrel, bicalutamide, and ivermectin [24]. These results indicated that the Kinetex column offered faster mass transfer with a flatter C term. It was suggested that this difference in performance was due to the Ascentis Express column has lower loading capacity and retention factor than even totally porous particles. The relation between the shell pore size and thickness was investigated to establish restricted diffusion of molecules [25]. The pore size was found to be the major contributor toward restricted diffusion of large protein molecules at 400 kDa, which was comparable to previous studies on the effect of pore size on molecules diffusion in totally porous particles]. The study involved the use of HaloC18 particles with pore sizes of 9, 16 and 40 nm for the separation of proteins such as myosin, ferritin, and _-amylase. Mass transfer kinetic could also be influenced by the shell thickness, thus the separation time almost halved by reducing shell thickness f 350 to150 nm. Narrow bore and capillary HPLC. In recent years, column miniaturization has been investigated and tested in order to achieve highly sensitive chromatography. The miniaturized columns are better for handling minute and/or dilute samples, especially in area such as forensic science and sport drug trails. The idea of miniaturization is to provide higher sensitivity and peak capacity than standard columns with minimal dead volume for small sample amounts [26]. Narrow bore columns of1–2 mm internal diameter (i.d.) can be used on a conventional HPLC system, but the instrument requires modification to reduce dead volume. This becomes more difficult when dealing with capillary columns as the pump needs to be adapted to accommodate low mobile phase flow valves. On-capillary sample injector and detection can be used to reduce dead volume [27]. Systematic studies on the efficiency between narrow bore and analytical type columns showed the same column performance, due to the packing and wall effect [28, 29]. Thus different packing methods have been applied such as dry packing [30], high-pressure slurry packing [31], and centripetal force packing [32] to overcome some of the issues. The majority of studies have been done using conventional 3–5 silica microspheres. Improved chromatographic performance was obtained by reducing particle size to 1.7 _m, but resulting in an increased backpressure. In this regard, core–shell particles can improve separation efficiencies and speed without having to use very small particles.

Comparative studies have been performed to determine the efficiency of narrow bore core–shell columns (2.1mm i.d.) with totally porous and monolithic columns [33]. The core–shell particle seemed to give better efficiency and peak asymmetry factors compared to monolithic columns. However, monolithic columns can still offer higher permeability and even lower backpressure higher linear velocities (up to 8.5 mm/s). This was the case when Kinetex vs. Chromolith columns were tested for isocratic separations of diastereoisomeric flavonoid compounds (silybin andacetylsilybin diastereoisomers). In another study, it was found that the performance of the porous shell particles was significantly negated by the extra-column band broadening especially in narrow bore columns (2.1mm i.d.) [34]. Gritt et al. carried out systematic studies using different type of core–shell particles and investigated the effect of internal diameter of the column on efficiency [35]. It was shown that depending on the type of silica investigated ,the 2.1 and 4.6 i.d. columns gave comparable efficiencies. How-ever, the effect on column efficiency became more dominating with decreasing particle sizes from 4.6 to 1.3m (reduced plate height increase slightly from 1.6 to 1.9, respectively) [35]. Currently there are fewer studies published on the application of core–shell particles in capillary columns. Most of those involve capillary electrochromatography. Fanali et al. used 100m i.d. capillary packed with 2.6m core–shell Kinetex C18 particles for the analysis of different brands of green and black tea constituents [36]. Sharper peaks in the chromatogram and shorter analysis time were observed, compared to sub-2 m C18 particles. Accurate mass detection of the tea constituents was determined by coupling with the mass spectrometer (MS). Due to the use of capillary column there was no need to split flow prior to the MS interface, hence resulted in better signal and sensitivity. In another study, phenyl-hexyl core–shell Phenomena particles were packed into capillary columns with 25, 50, 75, 100 and 150m i.d. to be used to separate five aromatic hydrocarbons [37]. Higher plate number per meter was obtained with decreasing capillary diameter without significant decrease of efficiency, with the highest plate number observed for 25m capillary. These results indicated that the extra band broadening observed with narrow bore columns were almost excluded in capillary columns.

HILIC separation Unbonded silica phase is used to increase retention of polar compounds such as carbohydrates, peptides and nucleic acid components. The separation can be carried out under hydrophilic interaction liquid chromatography (HILIC) condition [38, 39]. A Halo Penta-HILIC column demonstrated the ability for fast separation of a mixture of nucleosides and bases with excellent peak shapes and efficiency in less than 9 min [40]. It was also success-fully used for the analysis of abuse and metabolites drugs such ascocain, meperidine and methamphetamine. A comparative study with porous sub-2m and porous shell 2.7m was carried out under HILIC conditions. The fused-core column offered d a faster separation time and a backpressure two times lower, but generated 30% lower efficiency than predicted [41].The core–shell particles can be also used in supercritical fluid chromatography mode as it offers faster mass transfer and is environmentally friendly. A Kinetex HILIC column showed almost 50%increase in efficiency and halved the time of separation when com-pared with totally porous particles using gaseous CO2as the mobile phase [42].

Chiral separation Another area of chromatography is Chiral separation, which accounts for analysis of over one-third of marketed drugs. A few chiral phases are commercially available such as polysaccharides [43, 44], cylodextrines [45], and others [46]. A recent study reported the coating of Kinetex particles with polysaccharide chirals electrons. Higher selectivity was observed for the separation of enantiomers of trans-stilbene oxide, benzoin and 2,2-dihydroxyl-6,6_-dimethylbiphenyl. But the performance was relatively similar to totally porous particles. Wu et al. reported the bridging of chiral ligand in the porous shell with a diaminocyclohexane moiety. Rapid chiral separation was demonstrated. The column packed with the chiral core–shell particles exhibited better performance than the column packed with the functionalized periodic meso-porous organosilicas.4.5. Capillary electrochromatography separation Capillary electrochromatography (CEC) is a separation technique in which the mobile phase is driven by an electro-osmotic flow rather than pressure in HPLC. CEC combines the separation and selectivity of HPLC and the high efficiency of capillary electrophoresis (CE) [47]. The role of stationary phase has been investigated for improved separation. Variety of stationary phases has been tested such as silica and polymeric materials with different bonding phases [47-49]. Core shell particles have shown a great succession conventional liquid chromatography. However, the use of these particles in CEC is very limited so far. An interesting study by Fanaliet al. compared the performance of capillary columns packed with totally porous and core shell silica particles for chiral separation in CEC mode [50]. The particles were coated with cellulose tris(4-chloro-3-methylphenylcarbanate), which is a polymer-based chirals elector. The capillary column packed with the core shell 2.8 particles showed baseline separation of warfarin and temazpamwith excellent peak shapes compared to 3m totally porous particles. This study has shown that porous shell particles can perform in CEC mode without any loss of resolution or efficiency [50]. It would be interesting if these particles can be expanded into separation of other mixtures.

Two dimensional liquid chromatography two dimensional liquid chromatography (2D-LC) is a technique where the injected sample is analyzed by the use of two separation stages. This is accomplished by injecting the eluent from the first column onto a second column. While applications exist which utilize a pair of identical phases, the two phases do not necessarily need to be the same. With an alternate phase in the second column (or the second dimension), it becomes possible to separate analytes that are poorly resolved by the first column or to use the first dimension as a clean-up step. The main

advantage of this method over conventional one dimensional chromatography is the potential for a large increase in peak capacity. This can be achieved without requiring particularly efficient separations from either column as, under ideal conditions, it is possible to obtain a total peak capacity equal to the product of the first and second separations [51]. The major disadvantage is the long timescale involved incomprehensive 2D-LC. Run times can exceed several hours; how-ever theoretical peak capacities in the thousands can be achieved if a longer analysis time is acceptable [52, 53]. Examples of the use of fused core particles in 2D-LC include pharmaceutical and food analysis. In one study, the increased resolving power when using the reversed phase dual fused-core secondary columns confirmed the presence of minor components from the degradation of a drug compound. Very fast gradient separations were achieved at ambient temperature without excessive backpressure and without compromising optimal 1st dimension sampling rates [54]. In the analysis of pesticides in food, a totally porous HILIC column provided fast on-line clean-up of the samples in the first dimension, followed by analysis using a C18 core shell column. The method was shown to be capable of analyzing over 300 compounds with good sensitivity and robustness [55]. A layer of carbon could be deposited on 2.7m superficially porous silica microspheres without causing pore blockage. The use of these carbon clad core–shell silica as a new packing material in fast 2D-LCas the second dimension improved the peak capacity [56].

Using sol-gel processing techniques that incorporate nano structuring technology, a durable, homegeneous porous shell is grown on a solid silica core. This highly optimized process combined with industry leading column packing technology produces highly reproducible columns that generate extremely high plate counts.

Shashikant B et al., [57] developed a rphpc method on core shell column for the determination of Degradation and Process Related Impurities of Apixaban An Anticoagulant Drug The chromatographic separation was achieved on a Sigma-Aldrich's Ascentis Express® C18 (4.6 mm × 100 mm, 2.7 µ) HPLC column with a runtime of 40 min. Mobile phase A and mobile phase-B were phosphate buffer and acetonitrile respectively. The column oven temperature was set at 35°C and photodiode array detector was set at 225 nm. Nine process related impurities (Imp-1 to Imp-9) have been detected in test sample of Apixaban by using newly developed RP-HPLC method. Forced degradation study was carried out under acidic, alkaline, oxidative, photolytic and thermal conditions to demonstrate the stability-indicating nature of the developed RP-HPLC method.

Kamlesh K. Dutta et al., [58] Formulated a o triplet combined solid dosage film coated tablet containing amlodipine besylate (equivalent to 5mg amlodipine), hydrochlorothiazide (12.5mg) and losartan potassium (50mg) for the treatment of severe hypertension. Development and validated of a simple, fast, precise, selective and accurate HPLC method for the simultaneous determination of amlodipine besylate, hydrochlorothiazide and losartan potassium in the tablets. The formulation of the tablets was carried out as per standard protocols. The various steps involve in formulation were dispensing of raw materials, sieving, preparation of granulating solvent, mixing, granulation, drying (In FBD), lubrication, compression and coating. The separation of these three drugs was achieved on a Sun Shell C8 column (150 mm x 4.6 mm, 2.6 µm) with phosphate buffer-acetonitrile (70:30% v/v) as mobile phase at 1.0 mL/min flow rate and 230nm detection. Results and Conclusion: The physical parameters of tablets were satisfactory with average weight deviation from 3.23 to 3.29%, friability 0.04%, disintegration time 8.3 minutes, average hardness 85.43N and thickness from 3.92 to 4.01 mm. The assay was found to be 99.89%, 99.99% and 99.97% of amlodipine, hydrochlorothiazide and losartan potassium, respectively. The dissolution was found to be 98.8 to 99.70%, 97.85 to 98.95% and 97.98 to 99.99% of amlodipine, hydrochlorothiazide and losartan potassium, respectively. The uniformity of content was 99.85 to 99.99% and 99.60 to 99.99% of amlodipine and hydrochlorothiazide, respectively. The retention times observed were to be 7.338, 2.097 and 10.675 minutes for amlodipine besylate, hydrochlorothiazide and losartan potassium, respectively. The method was statistically validated for linearity, recovery, limit of detection, limit of quantification, accuracy.

Venkata Krishna Akula, et al., [59] development of a simple and precise HPLC method for the effective separation and quantitative determination of LCZ and its impurities. Experimental: Eight potential related impuritiesof LCZ were separated and identified in the bulk drug as well as oral solution dosage form. The separation was achieved on a core shell stationaryphase Kinetex biphenyl (250, 4.6×5 µm) column with mobile phase of sodium per chlorate in water and acetonitrile in a gradient elution. Results: The results were monitored and analytes were quantified at 230 nm. The method was validated as per ICH guidelines for specificity, linearity, precision, accuracy and robustness. The proposed method finds its application in the routine analysis of LCZ in bulk drug and various dosage forms.

Gamal H. Ragab, Hanaa M et al., [60] developed and validated a method for estimation of Tranylcypromine sulphate in bulk drug and in tablet dosage forms. Well- resolved peaks of target analyte and its degradation products were achieved on a Kinetex® column (75 mm x 4.6 mm ID) 2.6 µm at 30 °C, using simple isocratic mobile phase of acetonitrile - orthophosphoric acid 0.1 % (10: 90, v/v). The flow rate was 1.0 mL/min and the detection was performed at 220 nm. The retention time of the drug was 2 min while or the reported method was 6.7 min. The method was validated according to International Conference on harmonization (ICH) guidelines. Tranylcypromine was subjected to the stress conditions of hydrolytic acidic, basic, oxidative, and photolytic degradation. The assay was linear over the concentration range of 3-150 µg mL-1and the correlation coefficient was 1. The RSD% of inter and intraday precision was less than 1 %. The % recoveries were found to be 100.58 % proved that the proposed method is sufficiently accurate and precise. The method distinctly separates the drug from its degradation products within 2 min and total run time of 8 min.

Milagros Montemurro et al., [61] Methotrexate (MTX) is an anti neoplastic drug, and duetoits high toxicity, the therapeutic drug monitoring is strictly conducted in the clinical practice. The chemo metric optimization and validation of a high performance liquid chromatography (HPLC) method using core shell particles is presented for the determination of MTX in plasma during therapeutic monitoring. Experimental design and response surface methodology (RSM) were applied for the optimization of the chromatographic system and the analyte extraction step. A Poroshell120EC-C18 (3.0mm 75mm, 2.7µm) column was used to obtain a fast and efficient separation in a complete runtime of4 min. The optimum conditions for the chromatographic system resulted in a mobile phase consisting of acetic acid/ sodium acetate buffer solution (85.0 mM, pH¼4.00) and11.2% of acetonitrile at a flow rate of 0.4 mL/min. Selectivity, linearity, accuracy and precision were demonstrated in a range of 0.10–6.0 mM of MTX. The application of the optimized method requiredonly150 mL of b patient plasma and a low consumption of solvent to provide rapid results.

N Ben Omar, et al., [62] Therapeutic drug monitoring is an essential tool to optimize pharmacotherapy through relating drug concentration to two reference ranges: the therapeutic reference range and the dose related reference range. To achieve this purpose a specific method to determine the concentration of fluoxetine, desmethylfluoxetine, sertraline and desmethylsertraline in serum was developed. It was applied in routine TDM with adding a clinical pharmacological report using Konbest (computer program). Methods: The chromatographic separation was achieved on a core shell column with acetonitrile/methanol/potassium phosphate buffer as mobile phase in automated column-switching HPLC using an UV detector. All chemicals used were of HPLC grade. The drugs used were obtained from different pharmaceutical companies in Germany. Drug free serum was spiked with the standard stock solutions of drugs to get the final concentrations needed.

The later concentrations were then injected in the HPLC system. Results: The method was satisfactory; the compounds were well separated with a very good recovery. It was validated according to the recommendations of GTFCH (Gesellschaft für toxikologische und forensische Chemie). Conclusion: This method allows efficient and rapid determination of fluoxetine, sertraline and their metabolites in serum. It is practicable for the routine TDM and for the emergency cases. The Konbest information could guide the treatment of the patients.

## CONCLUSION

The noval core shell particles column technology plays impo rtance in liquid chromatography. This is due to core shell technologies p rovide a low pressure, high separation efficiency and it can reduces the a mount of analysis time without impacting an extreme back pressures. Co

re shell particles having high separation efficiency is largely due to more rapid analyte mass transfer from the mobile phase to the stationary pha se and the back again. This is because diffusion only occurs via the poro us outer layer of the particle rather than the entire particle. In terms of s ize and shape core shell particles are remarkably constant which also he lps to separation efficiency by limiting variable analyte movement withi n the particles .instead of investing any costly UPHPLC systems, it is bett er to improve the efficiency of their existing HPLC systems by using core shell technology.

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