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Analytical Techniques in Pharmaceutical Analysis: A Review

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Abstract: ***The development of the pharmaceuticals brought a revolution in human health. These pharmaceuticals would serve their intent only if they are free from impurities and are administered in an appropriate amount. To make drugs serve their purpose various chemical and instrumental methods were developed at regular intervals which are involved in the estimation of drugs.***

These pharmaceuticals may develop impurities at various stages of their development, transportation and storage which makes the pharmaceutical risky to be administered thus they must be detected and quantitated. For this analytical instrumentation and methods play an important role. This review highlights the role of the analytical instrumentation and the analytical methods in assessing the quality of the drugs. The review highlights a variety of analytical techniques such as titrimetric, chromatographic, spectroscopic, electrophoretic, and electrochemical and their corresponding methods that have been applied in the analysis of pharmaceuticals.

Keywords: Analytical Techniques; Titrimetry; Chromatography; Spectroscopy, Electrochemical methods.

I. INTRODUCTION

Guided by pharmacology and clinical sciences, and driven by chemistry, pharmaceutical research in the past has played a crucial role in the progress of development of pharmaceuticals.

The contribution of chemistry, pharmacology, microbiology and biochemistry has set a standard in the drug discovery where new drugs are no longer generated only by the imagination of chemists but these new drugs are the outcome of exchange of ideas between biologists and chemists.

The process of drug development starts with the innovation of a drug molecule that has showed therapeutic value to battle, control, check or cure diseases. The synthesis and characterization of such molecules which are also called active pharmaceutical ingredients (APIs) and their analysis to create preliminary safety and therapeutic efficacy data are prerequisites to identification of drug candidates for further detailed investigations (Valagaleti et al., 2003).

The investigations on the pre drug discovery are based on knowing the basic cause of the disease to be treated, the information on how the genes are altered that cause the disease, the interaction of proteins and the affected cells and changes brought by these affected cells and how they affect these cells.

Based on these facts a compound is developed which interacts with the affected cells and finally could become the drug molecule or active pharmaceutical ingredient (A.P.I) Drug discovery and Development, understanding the R&D process (http://www.phrma.org/sites/default/files/159/ rd_brochure_022307.pdf).

The ‘‘compound’’ which is set to become the drug molecule undergoes safety tests and a series of experiments to prove that it is absorbed in the blood stream, distributed to proper site of action in the body, metabolized sufficiently and demonstrates its non-toxicity thus, can be considered safe and successful.

Once the compound is finalized the preclinical research i.e. in vitro studies followed by the animal testing to check kinetics, toxicity and carcinogenicity tests are performed. After passing the pre-clinical tests the regulatory authorities grant permission for the clinical trials.

The clinical trials check whether the drug is working in the proposed mechanism or not, its optimum dose and schedule while the last two stages generate statistically important data about efficacy, safety and overall benefit–risk association of the drug. In this phase the potential interaction of the drug with other medicines is determined and monitors drug’s long term effectiveness. After a successful completion of the clinical trials, the drugs are launched in the market for patients. The summary of various stages of clinical trials are listed in Table 1.

Table 1Summary of phasewise clinical trial and motive of investigation.

Phase of clinical trail	Number and type of subjects	Investigation
Phase 1	50–200 healthy subjects (usually) or patients who are not expected to benefit from the IMP	Is the IMP safe in humans? What does the body do to the IMP? (pharmacokinetics) What does the IMP do to the body? (pharmacodynamics) Will the IMP work in patients?
Phase 2	100–400 patients with the target disease	Is the IMP* safe in patients? Does the IMP seem to work in patients?
Phase 3	1000–5000 patients with the target disease	Is the IMP really safe in patients? Does the IMP really work in patients
Phase 4	Many thousands or millions of patients with the target disease	Just how safe is the new medicine? (pharmacovigilance) How does the new medicine compare with similar medicines?

Source: guidelines in clinical trials: 2007 edition. The Association of the British Pharmaceutical Industry, 12 Whitehall London.

* IMP: investigational medicinal product i.e. the newly developed drug.

Development of single-enantiomer drugs was also made possible by asymmetric synthesis and chiral separation techniques. Several guidelines dealing with chiral drugs (FDA's, 1992; Health Canada, 2000; European Medicines Agency, 1996) have been published which encouraged the development of single enantiomer drugs for pharmaceutical manufacturers. The quality of chiral drugs was stipulated by the guideline of the International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) (ICH Topic Q 6 A,
1999). The guideline recommends applicants to consider other enantiomer as an impurity and to set the identity tests capable of distinguishing both enantiomers and the racemic mixture. It is required to provide tools for efficient quality systems ensuring safe and proper manufacturing processes (ICH, 2009). However, insufficient in-process control may result in the products suffering from surface irregularities (Akseli et al., 2008; Varghese and Cetinkaya, 2007). In addition, the finished products may contain unidentified foreign matter particles. The foreign matter has to be identified and its source should be defined in order to prevent further contamination. Hence it is required to provide an efficient detection and identification procedure of foreign matter from the dosage forms by utilization of analytical techniques (Pajander et al., 2013).

The drugs which are marketed may have different dosage forms. Formulation can be categorized according to the route of administration (Pifferi et al., 1999). Pharmaceutical development information provides the scientific rationale for formulation development and justification for a suitable dosage form. Regulatory guidance provides only limited details of the requirements for the data sets associated with the pharmaceutical development (U.S Department of Health, 2003) but more detailed information are available for the toxicological assessment of excipients (U.S Department of Health, 2002). Excipients are the major fraction of the solid dosage forms which serve as diluents to allow the formulation of appropriately sized tablets and coatings to protect the tablet from undesirable organoleptic qualities of the drug substance. Solid state reactions in the dosage form can occur when the drug substance is reactive and may be accelerated by physical and chemical interaction with excipients. In some cases excipients do not interact chemically but promotes the degradation of drug substance (Bryn et al., 2001). For example, primary and secondary amines can react with lactose, glucose and maltose to form glycosylamines (Serajuddin et al., 1999; Wirth et al., 1998).

In the field of pharmaceutical research, the analytical investigation of bulk drug materials, intermediates, drug products, drug formulations, impurities and degradation products, and biological samples containing the drugs and their metabolites is very important. From the commencement of official pharmaceutical analysis, analytical assay methods were included in the compendial monographs with the aim to characterize the quality of bulk drug materials by setting limits of their active ingredient content. In recent years, the assay methods in the monographs include titrimetry, spectrometry, chromatography, and capillary electrophoresis; also the electro analytical methods can be seen in the literature.

The present state-of-theart is replicated through the data in Table 2 based on the edition of European (The European Pharmacopoeia and Council of Europe, 2002) and US (United States Pharmacopoeia, 2004) pharmacopoeias.

From the stages of drug development to marketing and post marketing, analytical techniques play a great role, be it understanding the physical and chemical stability of the drug, impact on the selection and design of the dosage form, assessing the stability of the drug molecules, quantitation of the impurities and identification of those impurities which are above the established threshold essential to evaluate the toxicity profiles of these impurities to distinguish these from that of the API, when applicable and assessing the content of drug in the marketed products. The analysis of drug and its metabolite which may be either quantitative or qualitative is extensively applied in the pharmacokinetic studies.

Table 2 Proportion of various analytical methods prescribed for the assay of bulk drug materials in Ph. Eur. 4 and USP XXVII.

Method	Ph. Eur. 4 (%)	USP 27 (%)
HPLC	15.5	44
GC	2	2.5
Titration	69.5	40.5
Acid–base	57.5	29.5
Aqueous mixtures	21	5.5
Indicator	6.5	4.5
Potentiometric	14.5	1
Non-aqueous	36.5	24
Indicator	9.5	14
Potentiometric	27	10
Redox (Iodometry, Nitritometry, etc.)	6.5	5.5
Other (complexometry, argentometry, etc.)	5.5	5.5
UV–vis spectrophotometry	9.5	8.5
Microbiological assay (antibiotics)	3	2.5
Other (IR, NMR, polarimetry, fluorimetry, atomic absorption spectroscopy, polarography, gravimetry etc.)	0.5	2

Source: S. Gorog/Journal of Pharmaceutical and Biomedical Analysis 36 (2005) 931–937.

This review highlights the role of various analytical techniques and their corresponding analytical methods in the analysis of pharmaceuticals. 2. Analytical techniques

A. Titrimetric Techniques

Origin of the titrimetric method of analysis goes back to somewhere in the middle of the 18th century. It was the year 1835 when Gay–Lussac invented the volumetric method which subsequently leads to the origin of term titration. Although the assay method is very old yet there are signs of some modernization, i.e., spreading of non-aqueous titration method, expanding the field of application of titrimetric methods to (very) weak acids and bases as well as potentiometric end point detection improving the precision of the methods. With the development of functional group analysis procedures titrimetric methods have been shown to be beneficial in kinetic measurements which are in turn applied to establish reaction rates.

There are many advantages associated with these methods which include saving time and labor, high precision and the fact that there is no need of using reference standards. In the past titrimetric methods have been used for the determination of captopril (Rahman et al., 2005a), albendozole (Basavaiah and

Table 3 Chromatographic adsorbents: (approximate order is shown in the table, since it depends upon the substance being adsorbed, and the solvent used for elution).

Most strong adsorbent	Alumina	Al_2O_3
	Charcaol	C
	Florisil	MgO/SiO_2 (anhydrous)
Least strong adsorbent	Silica gel	SiO_2

Source: http://www.chem.wisc.edu/courses/342/Fall2004/TLC.pdf.

Prameela, 2003) and gabapentin (Sameer and Abdulrahman Basavaiah, 2011) in commercial dosage forms. Sparfloxacin (Marona and Schapoval, 2001) was determined by the nonaqueous titration method. In addition to its application in drug estimation titrimetry has been used in the past for the estimation of degradation products of the pharmaceuticals (Matei et al., 2008).

B. Chromatographic Techniques

1) Thin Layer Chromatography

Although an old technique yet it finds a lot of application in the field of pharmaceutical analysis. In thin layer chromatography, a solid phase, the adsorbent, is coated onto a solid support as a thin layer usually on a glass, plastic, or aluminum support. Several factors determine the efficiency of this type of chromatographic separation. First the adsorbent should show extreme selectivity toward the substances being separated so as to the dissimilarities in the rate of elution be large. For the separation of any given mixture, some adsorbents may be too strongly adsorbing or too weakly adsorbing. Table 3 lists a number of adsorbents in the order of adsorptive power.

Thin layer chromatography is a popular technique for the analysis of a wide variety of organic and inorganic materials, because of its distinctive advantages such as minimal sample clean-up, wide choice of mobile phases, flexibility in sample distinction, high sample loading capacity and low cost. TLC is a powerful tool for screening unknown materials in bulk drugs (Szepesi and Nyiredy, 1996). It provides a relatively high degree of assertion that all probable components of the drug are separated. The high specificity of TLC has been exploited to quantitative analytical purpose using spot elution followed by spectrophotometric measurement. TLC has been utilized for the determination of some steroids (Cimpoiu et al., 2006), pioglitazone (Gumieniczek et al., 2004), celecoxib (Bebawy et al., 2002) and noscapine (Ashour et al., 2009). TLC plays a crucial role in the early stage of drug development when information about the impurities and degradation products in drug substance and drug product is inadequate. Various impurities of pharmaceuticals have been identified and determined using TLC (White et al., 1992; Agbaba et al., 1996).

2) High Performance Thin Layer Chromatography

With the advancement of the technique, high performance thin layer chromatography (HPTLC) emerged as an important instrument in drug analysis. HPTLC is a fast separation technique and flexible enough to analyze a wide variety of samples. This technique is advantageous in many means as it is simple to handle and requires a short analysis time to analyze the complex or the crude sample cleanup. HPTLC evaluates the entire chromatogram with a variety of parameters without time limits. Moreover, there is simultaneous but independent development of multiple samples and standards on each plate, leading to an increased reliability of results. HPTLC has been used to quantitate drugs as ethinyl estradiol and cyproterone (Pavic et al., 2003), alfuzosin (Fayed et al., 2006) and tramadol and pentazocine (Ebrahim et al., 2011).

3) High-performance Liquid Chromatography (HPLC)

HPLC is an advanced form of liquid chromatography used in separating the complex mixture of molecules encountered in chemical and biological systems, in order to recognize better the role of individual molecules. It was in the year 1980, HPLC methods

appeared for the first time for the assay of bulk drug materials (United States Pharmacopoeia, 1980). As seen in Table 2, this has become the principal method in USP XXVII (United States Pharmacopoeia, 2004) and to a lesser extent but one of the most widely used methods also in Ph. Eur. 4 (The European Pharmacopoeia and Council of Europe, 2002).

The specificity of the HPLC method is excellent and simultaneously sufficient precision is also attainable. However, it has to be stated that the astonishing specificity, precision and accuracy are attainable only if wide-ranging system suitability tests are carried out before the HPLC analysis. For the reason the expense to be paid for high specificity, precision and accuracy is also high.

During the survey of the literature it was observed that among the chromatographic techniques HPLC has been the most widely used system. In liquid chromatography the choice of detection approach is critical to guarantee that all the components are detected. One of the widely used detectors in HPLC is UV detector which is capable of monitoring several wavelengths concurrently; this is possible only by applying a multiple wavelength scanning program. If present in adequate quantity, UV detector assures all the UV-absorbing components are detected.

A photodiode array (PDA) is a lined array of discrete photodiodes on an integrated circuit (IC) chip for spectroscopy. It is placed at the image plane of a spectrometer to allow a range of wavelengths to be sensed concurrently. When a variable wavelength detector (VWD) is used a sample must be injected numerous times, with changing wavelength, to be sure that all the peaks are detected. In the case of PDA, when it is used a wavelength range can be programed and all the compounds that absorb within this range can be identified in a single analysis. PDA detector can also analyze peak purity by matching spectra within a peak. PDA detector finds its application in the method development of Iloperidone in pharmaceuticals (Devi Manjula and Ravi, 2012).

The refractive index detector is the detector of choice when one needs to detect analytes with restricted or no UV absorption such as alcohols, sugars, carbohydrates, fatty acids, and polymers. Decent trace detection performance is secured through a low noise. This detector is having the lowest sensitivity among all detectors but suitable at high analyte concentrations. Lakshmi and Rajesh utilized the refractive index detector to analyze the content of volgibose in pharmaceutical formulations (Lakshmi and Rajesh, 2010). The electrochemical detector responds to the substances that are either oxidizable or reducible and the electrical output results from an electron flow triggered by the chemical reaction that takes place at the surface of the electrode. This detector was applied recently to analyze the content of glutathione in human prostate cancer cells and lung adenocarcinoma cells (Spadaro et al., 2011).

One of the most sensitive detectors among the LC detectors is fluorescence detector. Typically its sensitivity is 10–1000 times higher than that of the UV detector for strong UV absorbing materials used as an advantage in the measurement of specific fluorescent species in samples. One of the most important applications of fluorescence is the estimation of pharmaceuticals (Ulu and Tuncel, 2012). The application of various types of detector in HPLC is compared in Fig. 1.

Over a certain period of time most workers used the reversed-phase mode with UV absorbance detection whenever appropriate, because this provided the best available reliability, analysis time, repeatability and sensitivity. Several drugs have been assayed in pharmaceutical formulations (Siddiqui et al., 2010; Tang et al., 2012; Devika et al., 2012; Ahmed et al., 2012) and in biological fluids (Tariq et al., 2010; Samanidou et al., 2012; Malenovic´ et al., 2012; Giorgi et al., 2012) using HPLC. Thus, HPLC provides a major service in answering many questions posed by the pharmaceutical industry. However, the limitations of HPLC include price of columns, solvents and a lack of long term reproducibility due to the proprietary nature of column packing. Liquid chromatography combined with mass spectrometry (LC–MS) is considered as one of the most important techniques of the last decade of 20th century (Niessen, 1999). It became the method-of-choice for analytical support in many stages of quality control and assurance within the pharmaceutical industry (Ermer, 1998; Nicolas and Scholz, 1998). Recently HPLC-MS has been used for assay of drugs (Hilhorst et al., 2011; D'Avolio et al., 2010; Berset et al., 2010; Ding et al., 2006; Wren and Tchelitcheff, 2006; Zhou et al., 2011; Breaud et al., 2009). In addition to its application in analyzing the drugs HPLC alone and with hyphenated technique have been applied to analyze the impurities of the pharmaceuticals (Chitturi et al., 2011; Madireddy et al., 2011; Navaneeswari and Reddy, 2011; Thomas et al., 2012; Verbeken et al., 2011) and degradation products (Sabry et al., 2012; Hanysova et al., 2005; Bouchonnet et al., 2012).

4) Gas chromatography

Moving ahead with another chromatographic technique, gas chromatography is a powerful separation technique for detection of volatile organic compounds. Combining separation and on-line detection allows accurate quantitative determination of complex mixtures, including traces of compounds down to parts per trillions in some specific cases. Gas liquid chromatography commands a substantial role in the analysis of pharmaceutical product (Watson, 1999). The creation of high-molecular mass products such as polypeptides, or thermally unstable antibiotics confines the scope of this technique. Its main constraint rests in the comparative non-volatility of the drug substances therefore, derivatization is virtually compulsory.

Recently, gas chromatography has been used for assay of drugs such as isotretinion (Lima et al., 2005), cocaine (Zuo et al., 2004) and employed in the determination of residual solvents in betamethasone valerate (Somuramasami et al., 2011). Gas chromatography is also an important tool for analysis of impurities of pharmaceuticals. In recent years GC has been applied to estimate the process related impurities of the pharmaceuticals (Frost et al., 2003; Hiriyanna and Basavaiah, 2008), residual solvents listed as impurity by the International Conference of Harmonization are analyzed by the GC using a variety of detectors (Reddy and Reddy, 2009; Hashimoto et al., 2001; Saraji et al., 2012; Deconinck et al., 2012).

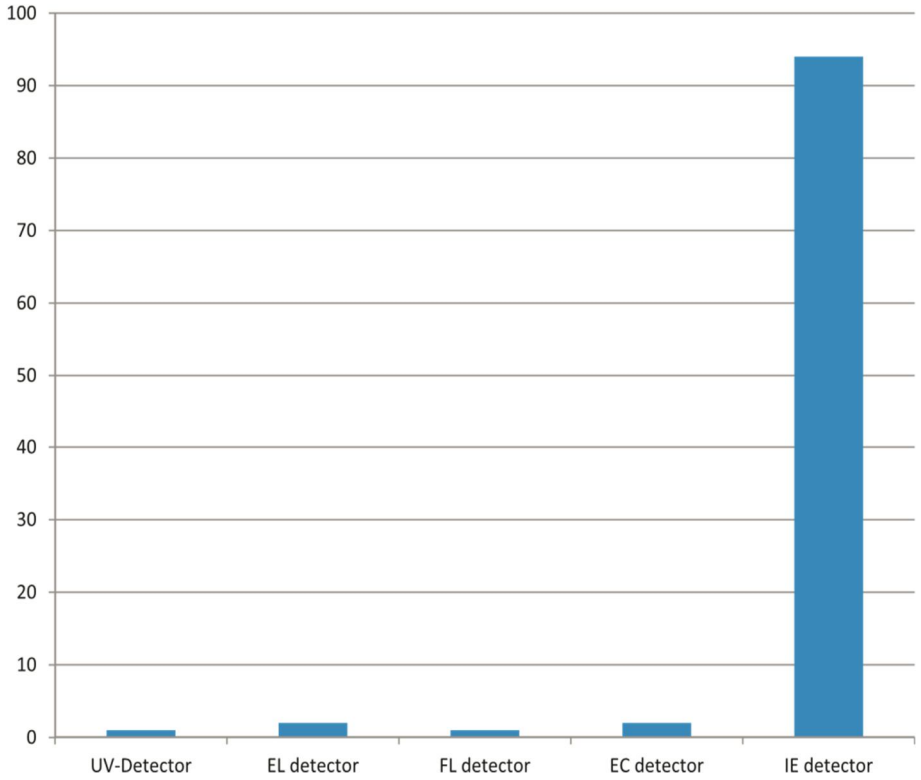

Figure 1 Usage of different detectors for HPLC analysis of drugs, Scale 0–100 represents use of the detector percentage. Source: R.N. Rao, V. Nagaraju. J. Pharm. Biomed. Anal. 2003, 33, 335–377.

C. Spectroscopic techniques

1) Spectrophotometry

Another important group of methods which find an important place in pharmacopoeias are spectrophotometric methods based on natural UV absorption and chemical reactions (Gorog, 1995). Spectrophotometry is the quantitative measurement of the reflection or transmission properties of a material as a function of wavelength.

The advantages of these methods are low time and labor consumption. The precision of these methods is also excellent. The use of UV–Vis spectrophotometry especially applied in the analysis of pharmaceutical dosage form has increased rapidly over the last few years (Tella et al., 2010; Venugopal and Sahi, 2005; Sharma et al., 2008; Ieggli et al., 2005). The colorimetric methods are usually based on the following aspects:

Complex-formation reaction.

Oxidation-reduction process.

A catalytic effect.

It is important to mention that colorimetric methods are regularly used for the assay of bulk materials. For example, the blue tetrazolium assay is used for the determination of corticosteroid drug formulations (Gorog and Szasz, 1978; Gorog, 1983).

The colorimetric method is also exploited for the determination of cardiac glycosides and is presented in European Pharmacopoeia. Several approaches using spectrophotometry for determination of active pharmaceutical ingredients in bulk drug and formulations have been reported and details of these methods are recorded in Table 4.

Table 4 Quantitative analysis of drugs in pharmaceutical formulations by UV–visible spectrophotometric procedures.

Reagent used	Name of drug	k_{max}	Reference
m-Cresol	Acetaminophen	640	Qureshi et al. (1992)
p-Chloranilic acid	Quetiapine fumarate	520	Vinay and Revenasiddappa (2012)
	Milrinone	519	Siddiqui et al. (2009)
2,3-Dichloro 5,6-dicyano1,4-benzoquinone	Duloxetine	477	Toker and Onal (2012)
	Amlodipine besylate	580	Rahman and Hoda (2003)
Chloranil	Dutasteride	525	Kumar et al. (2012)
	Lisinopril	520	Rahman et al. (2007)
7,7,7,8-Tetracyanoquinodimethane	Lisinopril	743	Rahman et al. (2005b)
	Alendronate sodium	840	Raza and Haq (2011)
Iodine	Flunarizine dihydrochloride	380	El Walily et al. (1995)
	Aripiprazole	400	Helmy et al. (2012)
Potassium iodide and potassium iodate	Irbesartan	352	Rahman et al. (2006a)
Ninhydrin	Pregabalin	402.6	Bali and Gaur (2011)
Ascorbic acid	Lisinopril	530	Rahman et al. (2005c)
Folin ciocalteu phenol	Oxcarbazepine	760	Gandhimathi and Ravi (2008)
	Ampicillin, amoxycillin, and carbenicillin	750, 770, 750	Ahmad et al. (2004)
Tris buffer	Diclofenac sodium	284, 305	Kramancheva et al. (1997)
Sodium metavanadate	Diltiazem HCl	750	Rahman and Azmi (2000)
Bromothymol blue	Rasagiline mesylate	414	Chennaiah et al. (2011)
Bromophenol blue	Rasagiline mesylate	414	Chennaiah et al. (2011)
Bromocresol green	Rasagiline mesylate	414	Chennaiah et al. (2011)
Potassium permanganate in alkaline medium	Isatin	60	AlOthman et al. (2013)
Brucine-sulfanilic acid in H_2SO_4 medium	Nicorandil	410	Rahman et al. (2004)
3-Methyl-2-benzothiazoline	Nicorandil	560	Rahman et al. (2004)
Cu (II) & eosin	Carbinoxamine	538	Ramadan and Mandil (2006)
Potassium ferricyanide and ammonium ferric sulfate	Pantoprazole sodium	725	Rahman et al. (2006b)
Chloramin T	Zidovudine	520	Basavaiah and Anil Kumar, 2007
	Verapamil HCl	425	Rahman and Hoda (2002)

Derivative spectroscopy uses first or upper derivatives of absorbance with respect to wavelength for qualitative investigation and estimation. The concept of derivatizing spectral data was first offered in the 1950s, when it was shown to have many advantages. However, the technique received little consideration primarily due to the complexity of generating derivative spectra using early UV–Visible spectrophotometers. The introduction of microcomputers in the late 1970s made it generally convincing to use mathematical methods to generate derivative spectra quickly, easily and reproducibly. This significantly increased the use of the derivative technique. The derivative method has found its applications not only in UVspectrophotometry but also in infrared (McWilliams, 1969), atomic absorption, fluorescence spectrometry (Snelleman et al., 1970; Konstantianos et al., 1994), and fluorimetry (O'Haver, 1976; John and Soutar, 1976). The use of derivative spectrometry is not restricted to special cases, but may be of advantage whenever quantitative study of normal spectra is problematic. Disadvantage is also associated with derivative methods; the differential degrades the signal-to-noise ratio, so that some form of smoothing is required in conjunction with differentiation (O'Haver and Begley, 1961).

2) Near Infrared Spectroscopy (NIRS)

Near infrared spectroscopy (NIRS) is a rapid and non-destructive procedure that provides multi component analysis of almost any matrix. In recent years, NIR spectroscopy has gained a wide appreciation within the pharmaceutical industry for raw material testing, product quality control and process monitoring. The growing pharmaceutical interest in NIR spectroscopy is probably a direct consequence of its major advantages over other analytical techniques, namely, an easy sample preparation without any pretreatments, the probability of separating the sample measurement position by use of fiber optic probes, and the expectation of chemical and physical sample parameters from one single spectrum.

The major pharmacopoeias have generally adopted NIR techniques. The European Pharmacopoeia in chapter 2.2.40 (The European Pharmacopoeia and Council of Europe, 2002) and United States pharmacopoeias (chapter 1119 United States Pharmacopoeia USP 26 NF 21, 2003) address the suitability of NIR instrumentation for application in pharmaceutical testing. NIR spectroscopy in combination with multivariate data analysis opens many interesting perceptions in pharmaceutical analysis, both qualitatively and quantitatively. A number of publications describing quantitative NIR measurements of active ingredient in intact tablets have been reported (Moffat et al., 2000; Alvarenga et al., 2008; Thosar et al., 2001; Ramirez et al., 2001; Blanco et al., 1996, 1999, 2000; Li et al., 2003; Molt et al., 1996; Buchanan et al., 1996; Merckle and Kovar, 1998; Eustaquino et al., 1998; Traford et al., 1999; Corti et al., 1999; Chen et al., 2001). In addition to the research articles many review articles have been published citing the application of the NIRS in pharmaceutical analysis (Luypaert et al., 2007; Blanco et al., 1998).

3) Nuclear Magnetic Resonance Spectroscopy (NMR)

Since the first report appeared in 1996 (Shuker et al., 1996) describing the use of NMR spectroscopy to screen for the drug molecules, the field of NMR based screening has proceeded promptly. Over the last few years, a variety of state-of-theart approaches have been presented and found a widespread application in both pharmaceutical and academic research. Recently NMR finds its application in quantitative analysis in order to determine the impurity of the drug (Mistry et al., 1999), characterization of the composition of the drug products and in quantitation of drugs in pharmaceutical formulations and biological fluids (Salem et al., 2006; Reinscheid, 2006), Many reviews on the application of NMR in pharmaceuticals have been published (Holzgrabe et al., 2005; MaletMartino and Holzgrabe, 2011).

4) Fluorimetry and phosphorimetry

The pharmaceutical industries continuously look for the sensitive analytical techniques using the micro samples. Fluorescence spectrometry is one of the techniques that serve the purpose of high sensitivity without the loss of specificity or precision. A gradual increase in the number of articles on the application of fluorimetry (Rahman et al., 2012, 2009) and phosphorimetry (De Souza et al., 2013; Chuan et al., 2000) in quantitative analysis of various drugs in dosage forms and biological fluids has been noticed in the recent past.

D. Electrochemical Methods

The application of electrochemical techniques in the analysis of drugs and pharmaceuticals has increased greatly over the last few years. The renewed interest in electrochemical techniques can be attributed in part to more sophisticated instrumentation and to increase the understanding of the technique themselves. Here the application of various electrochemical modes in the analysis of drugs and pharmaceuticals is presented in Table 5.

Table 5 Determination of drug by various electrochemical techniques.

Technique	Drugs determined	Remark	Reference
Voltammetry	b-blocker drugs	Nafion-coated glassy carbon electrode	Nigovic´ et al. (2011)
	Rosiglitazone	Square wave adsorptive stripping voltammetry	Al-Ghamdi and Hefnawy (2012)
	Leucovorin	Silver solid amalgam electrode	S˘ eles˘ovska´ et al. (2012)
	Secnidazole	Cathodic adsorptive stripping voltammetry	El-Sayed et al. (2010)
	Acetaminophen and tramadol	At glassy carbon paste electrode	Sanghavi and Srivastava (2011a)
	Dopamine	Differential pulse stripping voltammetry	Abdoljavadi and Masrournia (2011)
	Atenolol	Using nanogold modified indium tin oxide electrode	Goyal et al. (2005)
Polarography	Nifedipine		Jeyaseelan et al. (2011)
	Anti cancer drug, Vitamin K3		TasAˆ et al. (2011)
	Ciclopirox olamine		Ibrahim and El-Enany (2003)
Amperometry	Diclofenac		Gimenes et al. (2011)
	Verapamil		Ortuno et al. (2005)
Potentiometry	N-acetyl-L-cysteine		Prkic´ et al. (2011)
	Pentoxifylline		Alarfaj and El-Tohamy (2011)

Moreover, a large number of electroanalytical methods are available for quantification of pharmaceuticals. An amberlite XAD-2 and titanium dioxide nanoparticles modified glassy carbon paste was developed for the determination of imipramine, trimipramine and desipramine. The electrochemical behavior of these drugs was investigated using cyclic voltammetry, chronocoulometry, electrochemical impedence spectroscopy and adsorptive stripping differential pulse voltammetry (Sanghavi and Srivastava, 2013).The capsaicin modified carbon nanotube modified basal-plane pyrolitic graphite electrode or p-chloranil modified carbon paste electrodes have been developed for the determination of benzocaine and lidocaine. The electrochemically initiated formation of capsaicin-benzocaine adduct causes a linear decrease in the voltammetric signal corresponding to capsaicin which correlates to the added concentration of
benzocaine (Kachoosangi et al., 2008). A copper (II) complex and silver nanoparticles modified glassy carbon paste electrode was constructed and used for the determination of dopamine, levodopa,epinephrineandnorepinephrine.Theelectrochemical behavior of these drugs was studied using cyclic voltammetry, electrochemical impedance spectroscopy, chronocoulometry and adsorptive stripping square-wave voltammetry techniques (Sanghavi et al., 2013). The electrochemical behavior of clioquinol,a moleculewithalargespectrumofclinicalapplications, was studied by cyclic, differential pulse and square-wave voltammetry over a wide pH range using a glassy carbon electrode (Ghalkhani et al., 2011). Adsorptive stripping differential pulse voltammetric method has been developed for the determination of venlafaxine and desvenlafaxine using Nafion-carbon nanotube composite glassy carbon electrode (Sanghavi and Srivastava, 2011b). A carbon nanotube paste electrode modified in situ with Triton X 100 was developed for the individual and simultaneous determination of acetaminophen, aspirin and caffeine (Sanghavi and Srivastava, 2010). An electrochemical method based on potentiometric stripping analysis employing cryptand and carbon nanotube modified paste electrode has been proposed for the subnanomolar determination of bismuth (Gadharietal.,2010).Anovelmethod,capillaryelectrophoresis withamperometricdetection,hasbeenestablished forrapidand effective measurement of levodopa and bensevazide and its impurity (R,S)-2-amino-3-hydroxy propanohydrazide in cobeneldopa pharmaceutical formulations (Wang et al., 2005). Potentiometric stripping analysis of antimony based on carbon paste electrode modified with hexathia crown ether and rice husk has also been reported (Gadhari et al., 2011).

E. Kinetic Method of Analysis

Kinetic method of analysis has been developing since 1950s and yet in modern days it is taking a major resurgence in activity. The repetitive interest in the kinetic methods can be credited to the advancements made in principles, in automated instrumentation, in understanding the chemical and instrumentation, in data analysis methods and in the analytical application.
From the literature it is evident that the kinetic approach to analytical chemistry is rather general with several advantages over traditional equilibrium approach (Pardue, 1989; Mottola, 1988; Perez-Bendito and Silva, 1988). Essentially, kinetic methods trust the measurements of concentration changes (detected via signal changes) in a reactant (which may be the analyte itself) with time after the sample and reagents have been mixed manually or mechanically.
Going through the literature it can be evident that fixedtime and initial rate methods have been used more often for the determination of drugs in pharmaceutical formulations (Darwish et al., 2010; Rahman and Kashif, 2010). Automatic techniques for the kinetic methods are generally based on open systems, among the popular techniques are the stopped flow system (Andrade et al., 2010) and the continuous addition of reagent (CAR) technique (Jimenez-Prieto and Silva, 1998, 1999). Several drugs have been determined by using the CAR technique with photometric (Marquez et al., 1990) and fluorimetric detection (Marquez et al., 1989). The usage of catalysts to accelerate analytical reactions is feasible with both reaction rate and equilibrium estimations. The use of micellar media in kinetic method is recently encouraged to enhance the rate of reaction, through micellar catalysis and may additionally improve the sensitivity and the selectivity which in turn lessen the analysis time for the analyte (Monferrer-Pons et al., 1999; Pe´ rez-Bendito et al., 1999; Georgiou et al., 1991).
Multicomponent kinetic estimations, most often referred to as differential rate methods, are also receiving wide acceptance in the field of pharmaceutical research (Sultan and Walmsley, 1997). Two new approaches i.e. kinetic wavelength pair method (Pena et al., 1991) and H-point standard addition method (Givianrad et al., 2011) have been proposed for dealing with overlapping spectra of components in the binary mixtures.

F. Electrophoretic Methods

Another important instrument essential for the analysis of pharmaceuticals is capillary electrophoresis (CE). CE is a relatively new analytical technique based on the separation of charged analytes through a small capillary under the impact of an electric field. In this technique solutes are perceived as peaks as they pass through the detector and the area of individual peak is proportional to their

concentration, which allows quantitative estimations. In addition to pharmaceutical studies it finds an application in the analysis of biopolymer analysis and inorganic ions. CE analysis is generally more effective, can be performed on a quicker time scale, requires only a small amount, lesser up to Nano liter injection volumes, and in most cases, takes place under aqueous conditions. These four characteristics of CE have proven to be beneficial to many pharmaceutical applications. Several reports have appeared on the application of this technique in the routine drug analysis (Nehme´ et al., 2010; Zhang et al., 2009; Calcara et al., 2005). Different modes of capillary electrophoresis such as capillary zone electrophoresis (Hamoudora and Pospisilova, 2006; Nevado et al., 2006; Hauze et al., 2005; Ne´ meth et al., 2011; Amin et al., 2012), micellar electrokinetic chromatography (Hamoudova et al., 2006; Al Azzam et al., 2011; Theurillat et al., 2010), isotachophoresis (Pospisilova et al., 2005; Kubacak et al., 2005), capillary gel electrophoresis (Liu et al., 1995; Srivatsa et al., 1994), isoelectric focusing (Lasdun et al., 2001; Liu et al., 1996) and affinity capillary electrophoresis (Li et al., 2011; Martinez-Pla et al., 2004) have been developed and applied to pharmaceutical purity testing and in bio analysis of drugs.

G. Flow Injection and Sequential Injection Analysis

Laboratory automation was introduced in the second half of the XX century. Steward in the U.S. as well as Ruzicka and Hansen in Denmark, created the flow injection analysis (FIA) technique for the automation of chemical procedure (Stewart et al., 1976; Ruzicka and Hansen, 1975). The introduction of this technique approached to transform the conception of automation in chemical analysis by permitting instrumental measurement to be carried out in the absence of physical and chemical equilibria (Ruzicka and Hansen, 1988; Valcarcel and Luque de Castro, 1987; Karlberg and Pacey, 1989). The basis of Flow injection analysis (FIA) is injection of a liquid sample into a moving, non-segmented uninterrupted carrier stream of a suitable liquid. The injected sample forms a zone, which is then transported toward a detect or that uninterruptedly records the changes in absorbance, electrode potential, orotherphysical parameter resulting from the passage of the sample material through the flow cell. The stages of flow injection analysis have been shown in Fig. 2.

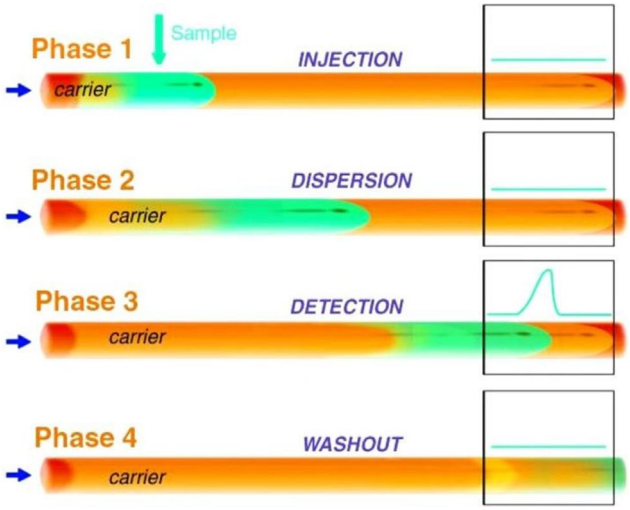

Figure 2 Stages of flow injection analysis. Source: http:// ww2.chemistry.gatech.edu/class/analyt/fia.pdf.

Following the broad application of computers in routine laboratory a second generation of flow analysis was offered by Ruzicka and Marshall (1990), who titled it as sequential injection analysis (SIA). As with the FIA, this is a non-segmented continuous flow arrangement based on the similar principle of controlled dispersion and reproducible manipulation of the FIA perception, but whose mode of operation is based on the theory of programmable flow.

The FIA technique has lent an significant contribution to the advancement of automation in pharmaceutical analysis and its advantages are well documented in several review articles (Karlicek et al., 1994; Calatayud et al., 1990; Calatayud and Garcia Mateo, 1992a,b; Evagen'ev et al., 2001; Fletcher et al., 2001) as well as in a specialized monograph (Calatayud, 1996).

The introduction of SIA has awakened the interest of the scientific community for automation in the pharmaceutical area (Christian, 1992). Many articles dedicated to pharmaceutical analysis have been published, including two review articles (Liu and Fang, 2000; Solich et al., 2004), applying sequential injection analysis to a wide variety of matrices, such as solid matrices, pastes (ointments,

creams), liquids (emulsions, suspensions, solutions) and covering various active ingredients with different healing activities. By profiting from the advantages in the economy of reagents and the elevated sampling rates, the majority of the applications are dedicated to the determination of active ingredients for quality control in pharmaceutical formulations.

H. Hyphenated Techniques

The coupling of a separation technique and on-line separation technique leads to the development of a hyphenated technique. The last two decades saw a remarkable advancement in the hyphenated techniques and its application in pharmaceutical analysis. A variety of hyphenated techniques such as LC-MS (Qian et al., 2012; Wang et al., 2012; Nandakumar et al., 2012), GC-MS (De Lima Gomes et al., 2011; Wollein and Schramek, 2012), LC-NMR (Lindon et al., 2000), CE-ICP-MS (Timerbaev et al., 2012) and CE-MS (Blasco et al., 2009) have been applied in the analysis of pharmaceuticals. The determination of drugs in biological materials is an important step in drug discovery and drug development. The determination of drugs in biological materials is an important step in drug discovery and drug development. HPLC together with various types of detection such as ultraviolet, fluorescence,and mass spectrometry has become the method of choice for bioanalytical method development (Nova´ kova´ et al., 2008). Recently a review of HPLC with UV or MS/MS‘ detection is presented for the analysis of meloxicam in biological samples and pharmaceutical formulations (Brezovska et al., 2013). Liquid chromatography-electrospray ionization–mass spectrometry method for the qualitative and quantitative determination of metabolites after oral administration of Rhizome coptidis and Zuojinwan preparation in rat urine has been developed (Rui et al., 2012), the same analytical technique was used for the simultaneous determination of L-ascorbic acid and acetyl salicylic acid in aspirin C effervescent tablet (Wabaidur et al., 2013). Urine samples were separated on a C_{18} column using a mixture of water (containing 0.1% formic acid) and acetonitrile (30:70 v/v) as the mobile phase. Recreational drug abuse is a growing issue and new substances are detected frequently in clinical and forensic samples. Diphenyl-2-pyrrolidinemethanol is one of these substances and therefore work has been done to identify it and its metabolites in rat urine using gas chromatography–mass spectrometry and liquid chromatography–high resolution–mass spectrometry (Meyer et al., 2013). Experiments were performed to identify the presence of human pharmaceuticals in the tropical aquatic environment of Malaysia. Water samples collected at different sites along the Langat River and effluents from five sewage treatment plants were extracted by solid phase extraction and analyzed using liquid chromatography coupled with tandem mass spectrometry (Al-Odaini et al., 2013). This study confirmed the presence of mefenamic acid, salicylic acid and glibenclamide in all river water samples. Drug–drug interaction of rabeprazole and clopidogrel in healthy Chinese volunteers has been studied. The plasma concentrations of rabeprazole and clopidogrel were analyzed by LC-MS/MS at different time intervals after administration (Wu et al., 2013). A novel LC-MS/MS method has been developed for the detection of carbapenemase activity from bacterial isolates (Peaper et al., 2013). A HPLC-MS/MS method has been reported for the determination of six kinds of parabens in food (Cao et al., 2013). The method was successfully applied to the determination of methyl, ethyl, propyl, butyl, isopropyl and isobutyl esters of 4-hydroxybenzoic acid. To assess the pharmacokinetics of selective substrates of human cytochrome P450s in mini pigs, caffeine, warfarin, omeprazole, metoprolol and midazolam were administered in combination either through intravenous route or orally. Plasma samples obtained upto 24 h after dosing were analyzed by liquid chromatography–tandem mass spectrometry to estimate typical pharmacokinetic parameters for each analyte (Mogi et al., 2012).

II. CONCLUSION

The main aim of the pharmaceutical drugs is to serve the human to make them free from potential illness or prevention of the disease. For the medicine to serve its intended purpose they should be free from impurity or other interference which might harm humans. This review is aimed at focusing the role of various analytical instruments in the assay of pharmaceuticals and giving a thorough literature survey of the instrumentation involved in pharmaceutical analysis. The review also highlights the advancement of the techniques beginning from the older titrimetric method and reaching the advanced hyphenated technique stages.

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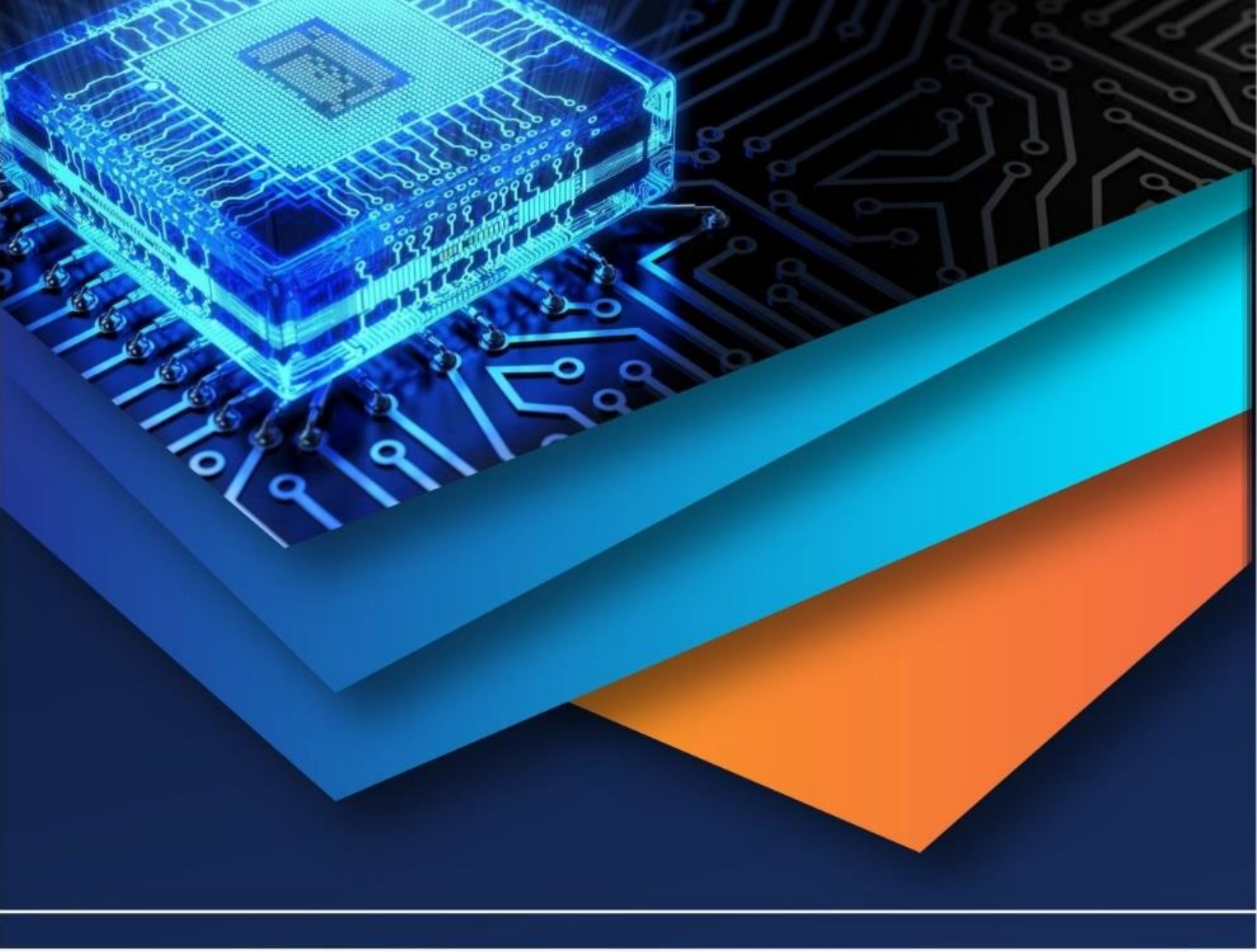

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