



RECENT ADVANCES IN ANALYTICAL TECHNIQUES

Editors:
Atta-ur-Rahman, *FRS*
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Recent Advances in Analytical Techniques

(Volume 5)

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PREFACE

This 5th volume of **Recent Advances in Analytical Techniques** contains five comprehensive chapters. The concepts described in this volume reflect the important recent advances in analytical chemistry including modern quality management aspects of these methods that can find wide use in industry. The chapters cover important recent trends in analytical methods, including the use of Liquid Chromatography-Based Mass Spectrometers in Chiral Analysis; New Trends in Sample Preparation for Pharmaceutical and Biological Analysis by Chromatographic Methods; Qualitative and Quantitative Investigation of Bio Tissues using Microscopy and Data Mining; Analytical Techniques for Analysis of Metals; and Minerals in Soil Samples and Monitoring Therapeutic Response in Cancers: A Raman Spectroscopy Approach. We hope that the readers will greatly enjoy reading the excellent chapters contributed by eminent scientists in their respective fields. We would like to thank all the authors that have contributed to this volume for their superb contributions. Also, we would like to thank the Bentham staff, including Ms. Mariam Mehdi (Assistant Manager Publications), and Mr. Mahmood Alam (Director Publications) at Bentham Science Publishers for their untiring efforts and efficient interactions with the authors in the publication process.

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CHAPTER 1

Superior Aspects of Liquid Chromatography-Based Mass Spectrometers in Chiral Analysis

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Abstract: Chirality has many important roles in life activities because enzymes, amino acids, nucleic acids, carbohydrates, fats, metabolic intermediates, and many other types of biomolecules are chiral. Due to the different properties of enantiomers, chirality is important in biological systems, and it is also critically important in many other fields, such as the pharmaceutical industry, chemical industry, petrochemical industry, food industry, and agrochemicals, particularly, medicine. Roughly 56% of the pharmaceuticals currently in use are chiral, and 88% of these are administered in racemic proportions, while single-enantiomer formulations of some marketed drugs have shown the higher potency of one stereoisomer compared to the other. Although they have the same chemical structures, most of the enantiomers present in racemic drugs have different pharmacokinetic, pharmacodynamic, biological, and toxic effects. The amounts of chiral molecules in different matrices are far below the levels required for the analysis of pharmaceutical preparations. Therefore, high resolution and sensitivity are needed to analyze chiral molecules. Mass spectrometers, which generally offer higher levels of sensitivity than conventional detection systems and accordingly allow the analysis of lower levels of analytes, have made large contributions to separation and detection science. Developments in new types of columns, different analysis modes, different matrices, and pharmaceuticals will be explored in this chapter. The parameters will be discussed with the pros and cons together with their applicability to different sample types.

Keywords: Bioanalysis, Biological Material, Chiral Analysis, Chiral Columns, Chirality, Enantiomers, ESI, GC-MS, IM-MS, LC-MS, Mass Spectrometer, MS/MS, Pharmaceutical Preparation, Plasma, QTOF-MS.

INTRODUCTION

Chirality is found in many areas of our life, from living systems to natural and synthetic organic substances. Chirality plays a dominant role in the interaction of molecules with biologically active substances, and it has created a new era in the

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development of the science branches. In other words, it has brought a third dimension to all fields of science.

Isomers are two or more different compounds that can be represented by the same molecular formula. These are compounds possessing the same molecular formulas while having different atomic arrangements. For this reason, the chemical structures of isomeric compounds also differ. This phenomenon can be examined within the two categories of structural isomers and stereoisomers. The latter are molecules possessing the same structure and differing only by their atomic arrangements. The covalent bonds and functional groups of a biomolecule are central to the function of that molecule. Stereochemistry is also known as the three-dimensional design of molecules (the prefix stereo- means “three-dimensionality”), and since the enantiomers of chiral molecules are optically active, they refract polarized light to the right and left. In particular, carbon atoms exist in the form of stereoisomers. Isomers can be divided into conformational and configurational isomers. “Enantiomer” is the name given to one of two stereoisomers, which is a mirror image of the other [1].

The word “chirality” has its origins in the Greek word “kheir,” which refers to the use of the right or left hand. Basically, chirality occurs when all the elements bonded to any element (mostly carbon atoms) are different from each other. A symmetrical center or axis does not exist and these molecules can occur in more than one form. In the most general form, chiral molecules have mirror images that do not coincide [2 - 4].

Molecules that cannot be superposed and are mirror images of each other, as stated above, are known as enantiomers. Since the enantiomers of chiral molecules are optically active, they refract polarized light to both the left and right. Therefore, there are two types of enantiomers, S-enantiomers and R-enantiomers, where the S and R come from the Latin words “sinister” and “rectus,” respectively, which mean left and right. Mixtures containing equal amounts of these enantiomers are called racemic [5, 6].

The development of chirality first started with the disintegration of the crystal molecule by Hauy in 1809. It became, even more, focal in 1848, when Louis Pasteur identified two crystals whose mirror images were asymmetric during the examination of tartaric acid crystals. Dr. J.H. van't Hoff discussed the specific arrangement of the four groups around the central carbon atom. Over time, the importance of these studies began to increase, and van't Hoff became the first scientist to receive a Nobel Prize in chemistry in 1901. In 1883, the concept of chirality had been fully expressed by Lord Kelvin with the following definition:

“If it does not coincide with the mirror image of a geometric shape or a group of points itself, it is called chiral” [7].

Chiral compounds have been widely used in industrial applications due to their various advantages. The reason why chirality is important for biological activity is that symmetry at the molecular level is dominant in biological processes [8]. In this sense, stereochemistry, the production of pharmaceutical products, and chiral properties are very prominent in determining the pharmacological effects of drugs. In particular, there is now significant interest in chiral separation for isolating and studying enantiomers. The chirality of molecules is important in the pharmaceutical field as well as in agriculture, food, electronics, and other applications. In addition to amino acid, enzyme, and hormone structures, chirality is also important in the plant, animal, and human life, and these molecules can be detected in living things by various methods, especially chromatographic methods.

Chiral drugs can display diverse characteristics in terms of their bioavailability, metabolism, distribution, and elimination, and they also possess qualitatively and quantitatively variable pharmacological and toxicological properties [9 - 11]. This attracts attention in the pharmaceutical market because of its superiority. Efforts to develop novel approaches for enantioselectively producing new chiral compounds are widely supported.

In the drug market, 88% of the drugs sold are mixtures consisting of racemates. Although they have identical chemical structures, the enantiomers present within racemic drugs generally possess varying characteristics in terms of their pharmacokinetics, pharmacodynamics, and biological and toxic effects. In its relevant guidelines, the US Food and Drug Administration (FDA) emphasizes that the physical effects of the different enantiomers present within racemic drugs need to be evaluated individually and that the design of novel chiral compounds as single enantiomers should be pursued [12]. It is possible that the enantiomers constituting drugs' active ingredients are different and more effective than the isomers. For example, in a finding now known in the medical literature as the thalidomide disaster, thalidomide's S-enantiomer exerts teratogenic effects, while the R-enantiomer has sedative properties [13]. Verapamil's R-enantiomer has applications as a multidrug resistance modulator in chemotherapeutics for the treatment of cancer, and the S-enantiomer has applications as a calcium channel blocker. At the same time, the R-enantiomer has been demonstrated to exert cardiotoxic effects [7]. Increases in cases like these have prompted researchers to consider drug molecules as chiral molecules and to focus on the production of single-enantiomer molecules whenever possible.

New Trends in Sample Preparation for Pharmaceutical and Biological Analysis by Chromatographic Methods

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Abstract: Sample preparation is the rate-limiting step in the success of an analytical methodology. It is needed not only to clean-up and concentrate the sample but to avoid the matrix effect and to protect high-cost equipment from deterioration. Therefore, an appropriate sample pretreatment procedure will improve method sensitivity and selectivity and increase analyte recovery to achieve a method of high precision and accuracy that will result in an overall improvement of the performance of the analytical system. The sample preparation method should be as simple as possible, with minute sample requirements, easily automatized, and versatile enough to be coupled to different types of equipment. The new trend in this topic also considers miniaturization without sacrificing performance and embraces the principles of green and sustainable chemistry to reduce the costs and consumption of solvents and reagents, devices corrosion, and excessive disposal. This chapter will review the most recent and innovative developments in sample preparation applied to pharmaceutical, environmental, and biological analysis, bearing in mind the above-mentioned characteristics to achieve an appropriate analytical performance.

Keywords: Carbon Sorbents, Imprinting, Magnetic Nanoparticles, Metal-Organic Frameworks Microextraction, Monoliths, Nanomaterials, Supramolecular Solvents.

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INTRODUCTION

In the last decade, the great technological advancement in the field of analytical chemistry instrumentation must necessarily be accompanied by innovative and strategic sample preparation methods that allow the design of analytical systems with high-quality standards that can be applied to the identification and quantification in challenging conditions, such as complex matrices and analytes in ultra-trace concentrations. Sample preparation is the rate-limiting step in the success of an analytical methodology. This is why it has been frequently defined as the “bottleneck” of an analytical system, as it is one of the main sources of errors and the most time-consuming step throughout the whole procedure. It is not only needed to clean up and concentrate the sample, but to avoid the matrix effect and to protect expensive equipment from deterioration. Therefore, without an appropriate sample pretreatment procedure, it would be impossible to assure result reliability. A suitable previous step to sample injection will improve method sensitivity and selectivity along with an increase in analyte recovery. This will provide a method of high precision and accuracy that will result in an overall performance improvement of the analytical system [1].

Traditional sample preparation techniques such as liquid-liquid extraction (LLE), dialysis or Soxhlet extraction have been used for decades to analyze different matrices [2]. However, nowadays, the principles of green chemistry that take into account environmental protection, as well as the need for miniaturization and automatization, challenge the use and validity of those traditional systems that, in addition to being laborious and highly operator-dependent, involve significant solvent, reagent and sample consumption.

This new concept in analytical developments, which undoubtedly calls for new work designs, necessarily impacts sample preparation as well. Therefore, in these modern times, sample pretreatment should be as simple as possible, with minute sample requirements, easy automatized, and versatile enough to be coupled to different types of equipment. The new trend in this topic also considers miniaturization without sacrificing performance and embraces the principles of green and sustainable chemistry in an effort to reduce solvent and reagent consumption, equipment corrosion and excessive disposal [3 - 5]. The concept and principles of green chemistry should also inspire pharmaceutical industry practices in terms of drug synthesis, processing, and manufacturing to move from conventional approaches to ecofriendly and sustainable alternatives [5].

Firstly, solid-phase extraction (SPE) was the technique that took a leap towards modernity, implementing notable advantages over LLE and overcoming several of its limitations. SPE simplicity, cost-effective instrumentation, high clean-up

capacity and concentration, medium exchange possibility, the versatility of its different stationary phases and automation at a later step, have positioned it as one of the preferred sample pretreatment techniques for many years. Undoubtedly, the core of SPE is the sorbent which influences selectivity, sample concentration, analyte sorptive capacity, clean-up efficiency as well as the format of the final SPE device. Analysts are always looking for new and versatile sorbent materials that could tackle upcoming challenges.

Later, due to miniaturization requirements, solid-phase microextraction (SPME) was developed. This miniaturized technique, with its characteristics of extraction-concentration-injection in a single step, no solvent needed, and reusable, was also considered as ecofriendly.

The terms “ecofriendly chemistry”, “green chemistry” or “clean chemistry”, among others, are used to define sustainable human practices in chemistry that rely on minimizing the consumption of hazardous chemicals, replacing them with benign ones and proper management of waste generation, improving operator’s safety, decreasing energy consumption, and reducing the impact of dangerous solvents on the environment. Modern analytical chemistry subscribes to the global changes regarding environmental awareness [3]. In this sense, SPME is considered to be the precursor of other micro and environmentally friendly techniques being the most remarkable: microextraction by packed syringe (MEPS), magnetic SPE (MSPE), dispersive SPE (DSPE), in-tube SPME (IT-SPME), solid phase nanoextraction (SPNE), stir bar-sorptive extraction (SBSE), stir bar-sorptive dispersive microextraction (SBSDME) and hollow fiber liquid-phase microextraction (HF-LPME).

Apart from the advances in sample pretreatment based on the use of solid sorbents such as those mentioned above, liquid-phase extraction has also evolved towards the use of minimal amounts of solvents by developing systems such as single-drop microextraction (SDME) and dispersive liquid-liquid microextraction (DLLME).

Other sustainable methodologies alternative to organic solvent extraction are subcritical water extraction (SWE), supercritical fluid extraction (SFE), ionic liquids (ILs), deep eutectic solvents (DES) and the use of surfactants and hydrotropes, which are considered as green solvents.

On the other hand, it is of great interest to mention membrane extraction procedures which are based on the use of solid or liquid polymers fixed between two other liquid or gaseous phases which combine and / or modify different techniques previously mentioned.

CHAPTER 3**Qualitative and Quantitative Investigation of Bio Tissues using Microscopy and Data Mining****Hafeez Ullah^{1,*}, Munir Akhtar¹ and Muhammad Ramzan Khawar¹**¹ *Biophotonics Imaging Techniques Laboratory, Institute of Physics, The Islamia University of Bahawalpur, Bahawalpur, Pakistan*

Abstract: The effects of glucose and salt on white blood cells, red blood cells, and platelets (PLTs) in the blood of a leukemic patient by using a white light microscope have been investigated for different concentrations (0 mM to 500 mM) of glucose and salt. It has been revealed that the shape of erythrocytes, leukocytes, and platelets changes and forms aggregates. Increasing the concentration of sodium chloride causes an increase in the rouleaux formation and aggregation of platelets. The comparison of CBC reports of these samples with and without analytes shows that total leukocyte count (TLC) decreases gradually towards normal ranges of leukocytes, which is favorable in the treatment of leukemia; at the same time, decreased level of hemoglobin HGB, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC) and increased level of red blood cell (RBCs) causes a reduction in the oxygen supply, which is in favor of cancer growth and anemia.

In the second set of work, a computer-aided system was planned for automatic classification of ultrasound kidney diseases and ultrasound liver (*i.e.*, cirrhosis). Two types of images were considered normal and chronic. By using the data mining technique, the statistical features were extracted to differentiate between normal and abnormal ultrasonic kidney images. By using feature extraction software (FES), a set of statistical features were extracted from the region of interest of each image at different frame rates. The data sets which were obtained using FES at different frame rates were then classified by using Weka. These extracted feature results were classified by using Weka and a 96.5% correct classification rate was obtained. The difference between the values of these features was useful to identify between normal and abnormal images.

Keywords: Abnormal image, Artificial neural networks, Complete blood count, Data mining, Erythrocytes, Feature extraction, Hyperglycaemia, Hypoglycaemia, Hypotonic solutions, Liver cirrhosis, Mean corpuscular hemoglobin, Mean corpuscular hemoglobin concentration, Red blood cell, Texture analysis, Total leukocyte count, Ultrasonic kidney, Ultrasound, Ultrasound images, White blood cell, White light microscopy, Whole blood.

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Novelty of the Work: The objective of this work was to measure the effects of glucose and salt level on white blood cells red blood cells and platelets (PLTs) in the blood of a leukemic patient by using a white light microscope. This work is a baseline for researchers to know about the physiology and state of blood components and parameters under hypernatremia.

INTRODUCTION

Blood: Blood is a fluid of connective tissue. Each 1 ml blood contains 40 - 45% cells and 50 - 55% plasma. Blood provides feasibility to transport different elements like oxygen, nitrogen, calcium, and minerals like salt, water, compounds of calcium, and ingredients of different foods in the form of energy in all parts of the body.

Two major components of blood are plasma and blood cells.

Plasma: It is a mixture of all things except white blood cells, red blood cells, and platelets. Usually, it contains electrolytes of different ions, such as Na^+ , Ca^+ and Cl^- , protein, vitamins, hormones, and other compounds. The normal volume of plasma is approximately 40 ml per kilogram of living body [1].

Blood Cells: There are three types of blood cells: red blood cells, white blood cells, and platelets.

i. Red blood cells or RBC are also called erythrocytes and occupy approximately 40 - 44 percent of every 1 ml of the blood. They transport oxygen to all parts of the body. The normal range of red blood cells is 4600000-5900000 cells per micro-liter.

ii. White blood cells are called Leukocytes; they are colorless like water. The normal range of leukocytes in young adults is 4000-11000 cells per microlitre [2a]. They defend the body from harmful microorganisms and serve as an army for the living body [2b].

iii. Platelets: the scientific term used for platelets is thrombocytes. These cannot be considered as cells because they lack a nucleus; they are very important in the formation of clots. The normal concentration of platelets in the blood is 150000-450000 cells/ μL . White blood cells and platelets are about 2% of the total blood volume [1, 2b].

Cancer: There are some specific rules of normal cell division; a disease in which cell division does not follow the normal rules of cell division is called cancer. It results in abnormal growth of organs or tissues. It is caused due to unfavorable changes in the DNA of cells. The spread of cancerous cells to other parts of the

body affects the normal function of these parts, and this process is called metastasis. If cancerous cells do not affect other parts of the body and remain in the place of origin, then this state is called benign. Approximately 90% of cancers are metastatic [2b, 3]. Generally, there are three fundamental types of cancer:

Carcinomas: Carcinoma is a type of cancer that starts in cells that make up the skin or the tissue lining organs, such as the breast, colon, skin, liver, and lungs. This is the most common form of cancer.

Sarcomas: A sarcoma is a type of cancer that starts in tissues like bone, muscle, or nerves.

Leukemias: It is the cancer of blood cells, especially white blood cells.

In this work, we have used the transmission mode of white light digital microscopy and dark field microscopy with a charge-coupled device (CCD) camera and recorded images for different molar concentrations of salt and glucose of leukemic blood slides. In white light microscopy, an intense beam of light is incident on the sample, an objective lens magnifies the cells, and we can observe cells or bodies through the eye-piece [2b].

MARROW OF BONE

Some bones in the body like ribs, skull, pelvis, and blades of shoulders have soft material inside them; this soft material is called marrow of the bone. It consists of all materials (like stem cells and fat cells *etc.*) related to the production of all types of cells in the body. Blood stem cell undergoes a process of continuous changes and is differentiated into red blood cell or platelet or white blood cell [2b, 4].

Hematopoietic Stem Cell

In the marrow of bone formation of blood cells, a special type of cells called hematopoietic stem cells is present. After mitosis, it is converted into two cells; one cell replaces the original cell while the other is converted into a blood cell after passing through a series of continuous changes. There is a fundamental difference between embryonic cell and hematopoietic stem cell; embryonic cell differentiates into any type of blood cells while hematopoietic cell only differentiates into any of the three types of blood cells, *i.e.*, white blood cell, red blood cell, or platelet. Precursors of blood cells remain in bone marrow, and when they become mature, they enter the blood. Instructions from the other cells in the marrow stimulate the process of new cell formation, and any disturbance during

CHAPTER 4

Analytical Techniques For Analysis of Metals and Minerals in The Soil Samples

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Abstract: Soils are the reservoirs of major, trace, and micro-nutrient elements. Determination of total metal content is important not only for geochemical application, but also for agriculture and environmental protection of living organisms. Determination of the total metal content is of interest for investigation of their mobility through the layers of soil, bioavailability for plant uptake, and animal/human consumption. In this chapter analytical techniques for analysis of metals from the soil samples are discussed. Quantitative analysis of the soil samples with fast and effective instrumental techniques such as atomic absorption spectroscopy (AAS), flame atomic absorption spectroscopy (F-AAS), graphite furnace or thermoelectric atomic absorption spectroscopy (GF-AAS, ET-AAS), inductively coupled plasma (ICP), neutron activation analysis (NAA), and X-ray fluorescence (XRF) are described for the application in soil analysis. The pretreatment methods and basic procedures for separation of different elements, such as sequential and selective extraction, as well as novel extraction techniques have been highlighted. The different instrumental techniques, used for the characterization of metal ions, have been examined in terms of their limits, accuracy, reproducibility, and precision.

Keywords: AAS, Analytical techniques in soil analysis, Chemical analysis of metals and metalloids, ICP, NAA, Soil, XRF.

INTRODUCTION

Soils and sediments represent a reservoir of different chemical elements of lithosphere. Due to the geochemical distribution and soil's genesis process, the availability of some metals is different. The composition of soil varies also due to the weathering processes and human activity. The major metals (elements) are

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found in the variable proportions in soils. Silicate minerals, as the most widespread group, contain elements from III and IV periods of the periodic table as major elements. These metals form basic oxides together with the alkaline metals (Na, K), earth alkaline metals (Ca, Mg), and transition metals (Fe, Al, Ti).

Metals into the soil can be found in three forms: 1) the soil solution, 2) absorbed to solid phases and 3) as part of the structure of solid phases [1]. Additionally, metal cations may be found in different physico-chemical forms, such as simple or complex ions, easily exchangeable ions, organically bounded, occluded by or coprecipitated with metal oxides and/or carbonates and/or phosphates, and secondary minerals, or as ions in crystal lattices of primary minerals [2]. Chemical compounds from the sediment may be carbonates, sulfides, silicates, hydroxides, phosphates, and organic substances in various stages of crystallization [3]. Major metals are, among the others, iron (Fe), magnesium (Mg), calcium (Ca), aluminum (Al), and manganese (Mn). Other metals whose concentration is less than 0.1% (1000 ppm) are characterized as trace elements [4].

Trace elements naturally exist in the soil. Some of them are essential micronutrients necessary for the development of both plants and animals. This group includes the following metals: cadmium (Cd), chromium (Cr), cobalt (Co), copper (Cu), gold (Au), lead (Pb), manganese (Mn), mercury (Hg), molybdenum (Mo), nickel (Ni), palladium (Pd), platinum (Pt), rhodium (Rh), silver (Ag), thallium (Tl), tin (Sn), vanadium (V), and zinc (Zn). Other important trace elements are metalloids (for example, B, As, and Sb), nonmetal (*e.g.*, Se) and halogen (*e.g.*, I and F) groups of elements [5]. Some metals are chemically bounded to a carbon atom, forming organometallic compounds, *e.g.*, organoarsenicals, organomercury, and organoleads compounds.

It is well known that some trace elements at elevated levels can be potential contaminants, namely heavy metals. These elements are: arsenic (As), boron (B), cadmium (Cd), chromium (Cr), copper (Cu), fluorine (F), lead (Pb), manganese (Mn), mercury (Hg), molybdenum (Mo), nickel (Ni), selenium (Se), and zinc (Zn). Heavy metals are well recognized as having a density greater than 6 g/cm³ [5]. They are highly toxic for the living organisms after exposure to the higher concentration.

Metals presented in the soil, especially trace elements, can be introduced by natural and anthropogenic sources too [6]. Their major natural sources are weathering (including erosion and deposition of wind-blow particles), eruptions of the volcanoes, forest fires, as well as biogenic sources. Anthropogenic sources, in turn, include aerial deposition, contamination from metal-smelting industries, transport emission, using commercial fertilizers and pesticides, disposal of sewage

sludge, and many others. Establishing a metal concentration from a normal soil compared with the contaminated soil is almost difficult. High concentrations of certain metals in the soils that are not considered to be contamination levels are the following (expressed as milligrams per kilogram of soil): 20 mg/kg Cu, 1 mg/kg for Cd, 50 mg/kg for Ni, 25 mg/kg for Pb, and 50 mg/kg for Zn [7]. Higher levels of some metals in the soil, which may be found as a consequence of the activity of humans, lead to increased health risk and environmental contamination [8].

From the chemical point of view, the concentration of the specific trace metals into the soil are very important for bioavailability and plant uptake [9, 10]. Plants mostly induce trace metals and micronutrients from the solid solution, so the effective availability of these elements depends of their solubility in the soil. Once absorbed by the plants, it effects the plant's life cycle. In the case of an elevated level of trace elements, bioavailability can be harmful for plant life. Therefore, determination of concentration of the specific elements into the soil is very important for agriculture [11] and environmental soil chemistry.

Quantitative speciation of the elements in the soil sample can be quite complex. Selecting the appropriate method and instrumental technique is of great importance for the chemical analysis of specific metals in soil. The aim of this chapter is to summarize the available methods for sampling, storage, and preparation of soil sample, pretreatments, as well as to put emphasis on the instrumental techniques suitable for monitoring and analysis of target metals.

CLASSIFICATION OF ANALYTICAL TECHNIQUES APPLIED FOR SOIL ANALYSIS

All analytical techniques for the analysis of metals into the soil can be divided into two major groups:

- A. Qualitative analysis – in which qualitative identification of metal cations is performed, *i.e.*, the presence or absence of a metal component is determined;
- B. Quantitative analysis - determines the quantitative presence of metals in a soil sample, *i.e.*, specifies the quantity of the metal cations that are present in the sample.

Quantitative Analysis

The majority of earlier analytical techniques are based on the measurement of weight or volume. These techniques are referred as *classical methods* for analysis. Other methods, which were developed after, are based on the measurement of some properties of the analyte (or the matrix containing the analyte), such as

Monitoring Therapeutic Response in Cancers: A Raman Spectroscopy Approach

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Abstract: Cancer is a multifactorial disease that is often asymptomatic and is thus detected at an advanced stage. Late detection and resistance to treatment are two of the major reasons for poor prognosis. The inherent limitations of conventional tools in evaluating therapeutic responses, raise the need to monitor such responses during treatment. Raman spectroscopy is a rapid, label-free, minimally invasive optical vibrational spectroscopy technique that has been widely employed for cancer detection. There is also significant literature on its applications in intraoperative surgical margin assessment, chemotherapeutic drug monitoring, and prediction of radiation response. However, most books and reviews focus on the diagnostic and screening applications of Raman spectroscopy. This chapter describes the role of Raman spectroscopy in the therapeutic monitoring of cancers and discusses its prospective applications. The present work provides a brief introduction to the basic principles of Raman spectroscopy, concise information on cancer aetiology, pathogenesis, diagnosis and therapeutics, and applications of Raman spectroscopy in the therapeutic monitoring of cancers. The role of Raman spectroscopy in monitoring conventional treatment modalities such as surgery, radiotherapy, and chemotherapy, along with novel treatment approaches such as immunotherapy and cold atmospheric plasma therapy, is discussed in detail. The chapter concludes with a brief introduction to the emerging field of Raman spectroscopy and artificial intelligence.

Keywords: Artificial Intelligence, Cancer, Cancer Field Effects, Cancer Therapy, Chemoresistance, Chemotherapy, Cold Atmospheric Plasma Therapy, Immunotherapy, Radioresistance, Radiotherapy, Raman Spectroscopy, Recurrence Prediction, Surgery, Surgical Margin, Therapeutic Drug Monitoring.

INTRODUCTION

Cancer is a multigenic, multicellular, and complex disease that is characterised by

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an incessant proliferation of cells. Determining the relationship between numerous alterations in cellular pathways and cancer progression is a challenging task. Moreover, treating a dynamic heterogeneous tumour cell population presents a formidable challenge for clinicians. Surgery, radiotherapy, and chemotherapy, either alone or in conjunction, are conventional treatment modalities for cancer. Chemotherapy and radiotherapy are also administered in neoadjuvant settings to achieve tumour shrinkage before surgery. The success of the treatment modalities is largely dependent on the stage of cancer, and an advanced stage is associated with poor prognosis. Hence, a substantial amount of research is oriented towards the early detection and diagnosis of cancer. However, as most patients have advanced-stage tumours, monitoring the therapeutic response is crucial to improve the efficacy of treatment and facilitate tailoring of their treatment regimen. Therapeutic monitoring is crucial in defining the course of treatment for non-responsive patients. Despite similar clinical and histopathological characteristics, a disparity in tumour response is routinely observed. Understanding the ineffectiveness of treatment or resistance to treatment in certain patients is limited by our current knowledge of tumour biology. Current techniques for monitoring treatment response include imaging modalities, assessment of tumour markers in biofluids, and cytological and histological evaluation of tumours. However, the inherent limitations of these techniques have led to the exploration of novel approaches, such as Raman spectroscopy. Raman spectroscopy, a rapid, label-free, non-invasive, non-destructive, optical vibrational spectroscopy technique, is a cost-effective alternative for monitoring treatment response in patients with cancer. It has been used for early diagnosis, biopsy guidance, surgery guidance, prediction of prognosis, surveillance of lesions, biomarker discovery, and therapeutic drug monitoring (TDM) in patients with cancer. Raman spectroscopy can identify subtle changes at the molecular level and provide a molecular fingerprint of the composition of a sample; hence, it has been increasingly explored for cancer diagnosis and treatment. In the following sections, we will briefly discuss the basics of Raman spectroscopy, cancer, and the applications of Raman spectroscopy in the therapeutic monitoring of cancers.

Raman Scattering

When light interacts with matter, small packets of light energy known as photons are absorbed, scattered, or transmitted. The frequency of light absorbed by a molecule depends on the difference between the ground and excited states of the molecule. Upon absorption of a photon, the molecule shifts to a higher energy excited state, and the change can be measured using absorption spectroscopy. During the interaction, the photons may scatter and can be detected at an angle relative to the incident light. The phenomenon of scattering is observed daily in

the changing colours of the sky. Sunlight is composed of a spectrum of coloured light. When the sun is high in the sky, the short-wavelength blue and violet light rays are scattered by molecules and particles in the atmosphere more efficiently than the longer-wavelength coloured rays, and the sky appears blue. In contrast, in the early morning and evening, the sun is low on the horizon, and sunlight must pass through more molecules and particles in the atmosphere. As the path length is longer, the short-wavelength blue and violet light rays are scattered out of sight, allowing the longer-wavelength red and yellow light rays to pass through; hence, the morning or evening sky is red, orange, and yellow. Scattering is dependent on the atmosphere; therefore, the exact opposite phenomenon is seen on Mars, which has a thin atmosphere that is mainly composed of carbon dioxide and dust particles. During the daytime, the Martian sky appears orange or reddish, while at sunset, it appears blue-grey. The scattering phenomenon that is responsible for the different colours of the sky is known as Rayleigh scattering. However, during the scattering process, a small fraction of light undergoes Raman scattering, which is useful for the identification of molecules.

In 1928, C.V. Raman and K.S. Krishnan experimentally demonstrated the inelastic scattering of light, a phenomenon called the Raman effect. However, Raman had also reported this phenomenon earlier as a weak residual fluorescence. The Raman effect had previously been predicted by Smekal in 1923 and theoretically described by Kramers and Heisenberg in 1925, Schrodinger in 1926, and Dirac in 1927. In 1930, Raman received the Nobel Prize for his discovery. In Raman and Krishnan's experimental approach, a beam of sunlight was focused by a telescope onto a purified liquid or dust-free vapour. A second lens was placed near the sample to collect the scattered radiation, and complementary light filters were used to detect the secondary radiation. Photographic plates were used to record the resulting spectra. A single spectrum for 600 mL of a pure liquid in a beaker was recorded over a 24 h period. Using 60 different liquids along with ether and amylene vapours, Raman and Krishnan demonstrated a new type of secondary radiation [1]. Raman reported that the scattering was feeble in comparison to ordinary scattering, indicating that Raman scattering is an inherently weak phenomenon occurring in only 1 in 10 million photons. However, modern instruments equipped with lasers, microscopes, and charge-coupled device (CCD) detectors have significantly enhanced the detection of Raman signals (Fig. 1).

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