EUROPEAN JOURNAL OF BIOMEDICAL AND PHARMACEUTICAL SCIENCES

http://www.ejbps.com

ISSN 2349-8870
Volume: 9
Issue: 1
173-187
Year: 2022

HYPHENATED BIO ANALYTICAL TECHNIQUES FOR CHEMOTHERAPEUTIC AGENTS OF CANCER THERAPY- A CRITICAL REVIEW

Seema Mehveen[1], Dr. Imam Pasha Syed*[1] and Anupama Koneru[2]

[1]Dept. of Pharmaceutical Quality Assurance, Sultan-ul-uloom College of Pharmacy, Mount Pleasant, #8-2-249, Road No.3, Banjara hills, Hyderabad-500034, Telangana, India.
[2]Dept. of Pharmacology, Sultan-ul-uloom College of Pharmacy, Mount Pleasant, #8-2-249, Road No.3, Banjara hills, Hyderabad-500034, Telangana, India.

***Corresponding Author: Dr. Imam Pasha Syed**
Dept. of Pharmaceutical Quality Assurance, Sultan-ul-uloom College of Pharmacy, Mount Pleasant, #8-2-249, Road No.3, Banjara hills, Hyderabad-500034, Telangana, India.

Article Received on 27/10/2021 **Article Revised on 17/11/2021** **Article Accepted on 07/12/2021**

ABSTRACT

This paper describes bio analytical method used for qualitative and quantitative estimation of anti-cancer molecules with hyphenated techniques. With the help of a proper interface, a hyphenated technique combines or couples two different analytical techniques. It is not always necessary to hyphenate between two techniques, such as separation or detection techniques. Authors for their proposed method mostly used protein precipitation for separating drug from bio-sample along with liquid liquid extraction. This paper also describes various types of cancers and their diagnosis in detail. This critical review focused on various types of columns used for separation along with detector.

KEYNOTES: Authors for their proposed method mostly used protein precipitation for separating drug from bio-sample along with liquid liquid extraction.

Introduction to Hyphenated Techniques

A hyphenated approach combines or couples two separate analytical methods using a proper interface. It is not necessarily necessary to hyphenate between two methods, such as separation and detection techniques. The trace element analysis industry has been revolutionised recently by the combination of more than two methods into an efficient integrated method. LC-NMR-MS instruments, also known as double hybrid instruments like LC-MS-MS, have recently become available and have been used to solve pharmaceutical problems. To create a powerful integrated system, such as SPE-LC-MS, online coupling with solid phase extraction (SPE), solid phase micro extraction, or large volume injection can be used. Separation-separation, separation-identification, and identification-identification techniques are all examples of hyphenated techniques.

LC-MS: Liquid chromatography mass spectrometry is a method that combines liquid chromatography with mass spectrometry to perform separation and mass analysis. The electrospray needle serves as a connection between liquid and mass chromatography.

Cancer

Cancer is a term used to describe a group of diseases characterised by uncontrolled cell division and irregular tissue development. The cell division mechanism in humans is very good at controlling and regularising cell differentiation and proliferation. When a mechanism called touch inhibition fails, uncontrolled cell division occurs. Cell replication stops in healthy organisms when cells come into contact with other cells during this process. As a result, contact inhibition becomes a potent anti-cancer mechanism, but in cancer cells it is lost. As a result, most cancers have tumours.

Types of Tumour:	1. Benign Tumour: These tumours are restricted to a specific part of the body. Furthermore, it is generally harmless and does not spread to other parts of the body. 2. Malignant Tumour: These tumours are cancerous, which means they will grow rapidly and spread to other body tissues. 3. Premalignant Tumour: This type of tumour may be benign, but it is observed to have malignant characteristics.
Types of Cancer:	1. Carcinoma: It is the most common type of cancer and is caused by epithelial cells. 2. Sarcoma: Connective tissues such as cartilage, fat, and bone tissues are the source of this substance. 3. Melanoma: Melanocytes, a type of pigment-containing cell, are the source of this pigment. 4. Lymphoma & Leukaemia: It comes from the cells that make up blood (such as b lymphocytes or white blood cells).
Causes of Cancer:	1. Physical factors: X-rays and gamma rays are examples of ionising radiation. 2. Chemical factors: Tobacco and smoke are examples. 3. Biological factors: Viral oncogenes, proto-oncogenes, and cellular oncogenes are all types of oncogenes.

Diagnosis of Cancer

Before cancer spreads to other parts of the body, it is critical to detect and diagnose it. Cancer genes must be identified in order to prevent cancer.

1. Lab Tests:	The presence of high or low levels of certain substances in your body can indicate the presence of cancer. As a result, lab tests that measure these substances in your blood, urine, or other bodily fluids can assist doctors in making a diagnosis. Abnormal lab results, on the other hand, are not always indicative of cancer.
2.Imaging Tests:	a) CT Scan: A CT scan is a procedure that involves taking a series of pictures of your organs from various angles using an x-ray machine connected to a computer. These images are used to create detailed 3-D images of your body's interior. b) MRI: An MRI takes pictures of your body in slices using a powerful magnet and radio waves. These slices are used to create detailed images of the inside of your body that can distinguish healthy from unhealthy tissue. c) Nuclear scan: A nuclear scan takes pictures of the inside of the body using radioactive material. This scan is also known as a radionuclide scan. d) Bone Scan: Bone scans are a type of nuclear scan that examines the bones for abnormalities or damage. They can be used to diagnose cancer that has spread to the bones or cancer that has spread to the bones. e) PET scan: A PET scan is a type of nuclear scan that produces detailed 3-D images of the areas of your body where glucose is absorbed. f) Ultrasound: Ultrasound examinations use high-energy sound waves that are inaudible to humans. The sound waves reverberate within your body's tissues. These echoes are used by a computer to create images of areas inside your body. A sonogram is the name for this image. g) X-rays: Low doses of radiation are used in X-rays to create images of the inside of your body. An x-ray technician will position you and guide the x-ray beam to the appropriate part of your body. You will need to remain very still while the images are taken, and you may need to hold your breath for a second or two.
3. Biopsy:	In most cases, a biopsy is required to diagnose cancer. A biopsy is a procedure in which a sample of tissue is removed by the doctor. A pathologist's findings are described in a pathology report, which includes information about your diagnosis.

Treatment of Cancer

1. Radiation therapy: Radiation therapy works in a completely different way. While chemotherapy administers drugs to the entire body, radiation aims to target only the cancerous cells in a specific area of the body, reducing the number of healthy cells affected during treatment. Instead of "killing" the cells directly, radiation damages the DNA of the cancer cells in question, causing them to die. While the treatment will have an effect on the healthy cells that surround the cancer cells, the healthy cells will usually repair the DNA damage and heal after treatment. When it comes to side effects, radiation therapy differs from chemotherapy in that it only affects the area that is being treated, and there is a risk of both early and late side effects. Early side effects usually appear during or soon after treatment and are short-lived, mild, and treatable. These are some of the most common early side effects of radiation therapy, according to the American Cancer Society:

- Fatigue
- Changes in the skin

- Side effects specific to a particular location, such as hair loss or mouth problems if radiation is received there.

Late side effects can appear months or even years later, depending on the area treated and the radiation dose used, and can occur anywhere the body has been exposed to radiation. The goal of any treatment plan is to reduce the risk of late effects as much as possible, so meticulous treatment planning is always our top priority.

Radiation Therapy and Chemotherapy are used to treat cancer in the following ways: No two bodies or cancers are alike. There should be no one-size-fits-all approach to cancer treatment. While both chemotherapy and radiation therapy is intended to treat and fight cancer, they do so in different ways. Because each person's body and type of cancer respond to treatment differently, having access to some of the most advanced treatments, technologies, research, physician specialists, and a whole-person approach to care becomes so important. Some patients may only receive chemotherapy or radiation therapy, while others may receive a combination of the two, as well as additional treatments like immunotherapy, more personalised medicine, or clinical trials. All of these things are things that our cancer experts assist patients with on a daily basis in order to provide the best possible cancer treatment, recovery, and cure outcomes.

2. Chemotherapy: Chemotherapy is distinguished by two main characteristics. To begin, it employs specialised drugs that are designed to target and kill rapidly dividing cells (like cancer cells). Second, because these drugs work throughout the body rather than just one part, they can prevent cancer cells from spreading to other parts. Chemotherapy can cause side effects outside of the cancer's location because it affects all cells in the body. While each type of chemotherapy has its own set of risks and side effects, each person will respond differently to treatment. According to the American Cancer Society, the following are some of the most commonly reported side effects of chemotherapy:

- Fatigue
- Hair loss
- Easy bruising and bleeding
- Infection
- Anemia (low red blood cell counts)
- Nausea and vomiting
- Appetite changes
- Constipation
- Diarrhea
- Mouth, tongue, and throat problems such as sores and discomfort when swallowing
- Nerve and muscle problems such as numbness, tingling, and pain
- Skin and nail changes such as dry skin and colour shift
- Urine and bladder changes as well as kidney issues
- Weight fluctuations
- Chemo brain, which causes symptoms such as decreased concentration and focus
- Mood swings
- Changes in libido and sexual function
- Fertility issues

Chemotherapy comes in a variety of shapes and sizes. It can be administered as an outpatient procedure in a hospital, doctor's office, or even at home via IV, oral administration, injection, or direct skin application.

a) Types of Chemotherapy

Alkylating Agents:	❖ Mustard gas derivatives: Mechlorethamine, Cyclophosphamide, Chlorambucil, Melphalan, and Ifosfamide. ❖ Ethylenimines: Thiotepa and Hexamethylmelamine. ❖ Alkylsulfonates: Busulfan. ❖ Hydrazines and Triazines: Altretamine, Procarbazine, Dacarbazine and Temozolomide. ❖ Nitrosureas: Carmustine, Laromustine and Streptozocin. Nitrosureas are unique because, unlike most types of chemo treatments, they can cross the blood-brain barrier. They can be useful in treating brain tumors. ❖ Metal salts: Carboplatin, Cisplatin, and Oxaliplatin.
Plant Alkaloids:	❖ Vinca alkaloids: Vincristine, Vinblastine and Vinorelbine. ❖ Taxanes: Paclitaxel and Docetaxel. ❖ Podophyllotoxins: Etoposide and Tenisopide. ❖ Camptothecan analogs: Irinotecan and Topotecan.
Antitumor Antibiotics:	❖ Anthracyclines: Doxorubicin, Daunorubicin, Epirubicin, Mitoxantrone, and Idarubicin. ❖ Chromomycins: Dactinomycin and Plicamycin. ❖ Miscellaneous: Mitomycin and Bleomycin.
Antimetabolites:	❖ Folic acid antagonist: Methotrexate. ❖ Pyrimidine antagonist: 5-Fluorouracil, Foxuridine, Cytarabine, Capecitabine, and Gemcitabine. ❖ Purine antagonist: 6-Mercaptopurine and 6-Thioguanine. ❖ Adenosine deaminase inhibitor: Cladribine, Fludarabine, Nelarabine and Pentostatin.
Topoisomerase	❖ Topoisomerase I inhibitors: Ironotecan, topotecan

Inhibitors:	❖ Topoisomerase II inhibitors: Amsacrine, etoposide, etoposide phosphate, teniposide
Miscellaneous Antineoplastics:	❖ Ribonucleotide reductase inhibitor: Hydroxyurea. ❖ Adrenocortical steroid inhibitor: Mitotane ❖ Enzymes: Asparaginase and Pegaspargase. ❖ Antimicrotubule agent: Estramustine ❖ Retinoids: Bexarotene, Isotretinoin, Tretinoin (ATRA)

CHEMOTHERAPY
LITERATURE REVIEW

1. Wenxuan He et.al reported LC-MS/MS method for simultaneous quantification of Cyclophosphamide and Doxorubicin with the title "A Simple and Sensitive LC-MS/MS Method for the Simultaneous Determination of Cyclophosphamide and Doxorubicin Concentrations in Human Plasma" is described as follows: Authors reported a method for the LC-MS/MS determination of cyclophosphamide and doxorubicin concentrations in patient plasma, following intravenous chemotherapy using protein precipitation without time-consuming supernatant drying and reconstitution steps, at the same time using a HILIC pre-column to further remove residual phospholipids. The method has a less than 15% RE and less than 5% RSD both intra- and inter- day.[1]

2. Noushin Rastkari et.al reported GC-MS method for simultaneous quantification of Cyclophosphamide and Ifosphamide with the title "Rapid Method for the Determination of Cyclophosphamide and Ifosphamide in Urine at Trace Levels by Gas Chromatography-Mass Spectrometry" is described as follows: A rapid and simple method for the simultaneous extraction of CP and IP from human urine has been developed using liquid-liquid extraction. The detection limits of cyclophosphamide and ifosphamide in urine samples were 0.5 and 1 ng ml−1, respectively, with a signal-to-noise ratio of 3:1. The regression correlation coefficients (r2) were over 0.99 in all experiments. This method is sensitive enough to determination of low levels of CP and IF in a range of urine concentrations relevant to performing low exposure assessment.[2]

3. Asmae Mirkou et.al reported LC-MS/MS method for simultaneous quantification of Melphalan with the title "Assays for the quantification of melphalan and its hydrolysis products in human plasma by liquid chromatography-tandem mass spectrometry" is described as follows: Two high-performance liquid chromatography tandem mass spectrometry (LC-MS/MS) assays are described for the quantification of melphalan in human plasma. N-phenyldiethanolamine was tested as internal standard. The first assay consisted of a protein precipitation by cold methanol and a reversed-phase HPLC whereas the second one was based on a solid phase extraction and a hydrophilic interaction chromatography. Both provided a very satisfactory mean extraction yield with a small volume of sample. The first method was simple, rapid and used as a routine assay. The second one was developed in order to determine melphalan hydrolysis products and to avoid scarce cases when interferences from biological matrix alter the quantification of melphalan using the first method. The two assays were linear and sensitive in the range of 1-500ng/mL for the first one and in a range of 25-2000ng/mL for the second one. Concentrations out of the range fixed with the first method were also validated. The procedure was reliable with precision and accuracy below 10%. All compounds were detected after positive mode electrospray ionization in selected reaction monitoring mode. These new analytical procedures were developed for melphalan pharmacokinetic studies or therapeutic drug monitoring.[3]

4. Ala F Nassar et.al reported LC-MS/MS method for simultaneous quantification of Laromustine with the title "Development and Validation of LC–MS-MS Assay for the Determination of the Emerging Alkylating Agent Laromustine and Its Active Metabolite in Human Plasma" is described as follows: The objective of this study was to validate a method for the determination of laromustine (VNP40101M) and short-lived its active metabolite (VNP4090CE) that has a half-life in human blood of <90 s in human plasma by liquid chromatography (LC) with tandem mass spectrometric (MS/MS) detection. Authors have overcome the stability dilemma by acidified the human plasma with citric acid. Laromustine "breaks" down on the source of mass spectrometry to give m/z 249 which is the same m/z for VNP4090CE. Because VNP4090CE and laromustine elute at approximate retention time of 1.93 and 2.94 min, respectively, authors were able to quantify both of them in one method. VNP40101M, VNP4090CE and the internal standards were extracted from human plasma by liquid–liquid extraction into ethyl ether. The ethyl ether layer was evaporated, reconstituted and analyzed using LC with MS/MS detection. Validation parameters such as selectivity, limit of quantitation, linearity, precision, accuracy, recovery, autosampler viability, freeze–thaw cycles and compounds stability are evaluated for this method. Results were calculated using peak area ratios, and calibration curves were generated using a weighted (1/x2) linear least-squares regression. Calibration curves for VNP40101M and VNP4090CE in human plasma ranged from 1.00 to 1,000 ng/mL. In this study, both intra- and inter-assay results demonstrated a relative standard deviation for calibration standards (inter-assay) and quality control samples (intra- and inter-assay) to be ≤15.0%. In this method, there is ~1.79% isotopic interference of VNP40101M to VNP40101M-IS, and ~3.76% isotopic interference of VNP4090CE to VNP4090CE-IS. It was concluded that there was no significant carryover.[4]

5. Romain Guilhaumou et.al reported LC-MS/MS method for simultaneous quantification of Vincristine with the title "Validation of an electrospray ionization LC/MS/MS method for quantitative analysis of vincristine in human plasma samples" is described as follows: A sensitive and specific liquid chromatography-tandem mass spectrometry (LC/MS/MS) method was developed for the quantification of vincristine in plasma in order to investigate pharmacokinetics in a paediatric population. Two hundred microliters of plasma was added to vinblastine, used as internal standard. Chromatographic separation was achieved on a C8 HPLC column (Phenomenex Luna 50 mm x 2.0 mm, 3.0 microm) with a mobile phase gradient at a flow rate of 0.2 ml/min. Quantification was performed using the transition of 825.4-->765.4 (m/z) for vincristine and 811.4-->751.4 (m/z) for vinblastine. Chromatographic separation was achieved in 8 min. The limit of quantification was 0.25 ng/ml with a precision of 10.2% and an accuracy of 99.6%. The calibration curve was linear up to 50.0 ng/ml. Intra-day precision and accuracy ranged from 6.3% to 10% and from 91.9% to 100.8%, respectively. Inter-assay precision and accuracy ranged from 3.8% to 9.7% and from 93.5% to 100.5%, respectively. No significant matrix effect was observed for vincristine. A rapid, specific and sensitive LC/MS/MS method for quantification of vincristine in human plasma was developed and is now successfully applied for pharmacokinetic studies in paediatric patients.[5]

6. G. Corona et.al reported LC-MS/MS method for simultaneous quantification of Vincristine with the title "Rapid and sensitive analysis of vincristine in human plasma using on-line extraction combined with liquid chromatography/tandem mass spectrometry" is described as follows: A simple and rapid method has been developed and validated for the quantitation of vincristine in human plasma by liquid chromatography/tandem mass spectrometry (LC/MS/MS) with atmospheric pressure chemical ionization using on-line solid-phase extraction. The method uses vinblastine as internal standard and the sample preparation is limited just to a plasma protein precipitation step. Further sample clean-up is carried out on-line through a perfusion column preceding an analytical phenyl LC column, the latter directly connected to the mass spectrometer. Quantitation is performed in multiple reaction monitoring mode using the transitions of m/z 825.3 --> 765.3 and 811.3 --> 751.3 for vincristine and vinblastine respectively. The assay was linear (r2 > or =0.99) in a concentration range from 0.1 to 500 ng/mL. Carry-over, measured on the experimental set-up, was less than 0.04%. Recovery for vincristine and the internal standard was within 90-95%. The intra-day and inter-day assay precision ranged from 1.2% to 6.8% RSD while mean percentage deviation from nominal value ranged from 0.01% to 6.1%. The proposed assay was found suitable for pharmacokinetics investigations and clinical therapeutic drug monitoring especially in pediatric cancer patients.[6]

7. Fen Yang et.al reported UPLC-MS/MS method for simultaneous quantification of Vincristine with the title "Validation of an UPLC–MS-MS Method for Quantitative Analysis of Vincristine in Human Urine After Intravenous Administration of Vincristine Sulfate Liposome Injection" is described as follows: Authors have developed and validated a method to quantify VCR in human urine to obtain the urinary excretion of VCR after intravenous administration of VSLI. The analyte was extracted from urine samples using liquid–liquid extraction after addition of vinblastine (VBL, used as internal standard) and chromatographed on an Acquity UPLC HSS T3 column with a gradient mobile phase at a flow rate of 0.4 mL/min. The multiple reactions monitoring transitions of m/z 413.2 → 353.2 and m/z 406.2 → 271.6 were used to quantify VCR and VBL, respectively. The lower limit of quantification was 0.5 ng/mL with a precision (RSD%) of 5.7% and an accuracy (RE%) of 6.7%. The calibration curve was linear up to 100.0 ng/mL. Intraday precision and accuracy ranged from 0.8 to 11.0% and from −12.4 to 11.3%, respectively. Interassay precision and accuracy ranged from 8.0 to 10.1% and from −7.7 to 3.6%, respectively. No significant matrix effect was observed for VCR. The method was successfully applied for pharmacokinetic study of VSLI to investigate the route and extent of VCR urinary excretion in Chinese subjects with lymphoma.[7]

8. Liia D. Vainchtein et.al reported LC-MS/MS method for simultaneous quantification of Paclitaxel with the title "A simple and sensitive assay for the quantitative analysis of paclitaxel and metabolites in human plasma using liquid chromatography/tandem mass spectrometry" is described as follows: A sensitive and specific LC-MS/MS assay for the determination of paclitaxel and its 3′p- and 6-α-hydroxy metabolites is presented. A 200 µL plasma aliquot was spiked with a 13C6-labeled paclitaxel internal standard and extracted with 1.0 mL tert-butylmethylether. Dried extracts were reconstituted in 0.1 m ammonium acetate–acetonitrile (1:1, v/v) and 25 µL volumes were injected onto the HPLC system. Separation was performed on a 150 × 2.1 mm C18 column using an alkaline eluent (10 mm ammonium hydroxide–methanol, 30:70, v/v). Detection was performed by positive ion electrospray followed by tandem mass spectrometry. The assay quantifies a range for paclitaxel from 0.25 to 1000 ng/mL and metabolites from 0.25 to 100 ng/mL using 200 µL human plasma samples. Validation results demonstrate that paclitaxel and metabolite concentrations can be accurately and precisely quantified in human plasma. This assay is now used to support clinical pharmacologic studies with paclitaxel.[8]

9. Bianca Posocco et.al reported LC-MS/MS method for simultaneous quantification of Paclitaxel with the title

"A new high-performance liquid chromatography-tandem mass spectrometry method for the determination of paclitaxel and 6α-hydroxy-paclitaxel in human plasma: Development, validation and application in a clinical pharmacokinetic study" is described as follows: The developed method used a small volume of plasma sample and is based on quick protein precipitation. The chromatographic separation of the analytes was achieved with a SunFire™ C18 column (3.5 µM, 92 Å, 2,1 x 150 mm); the mobile phases were 0.1% formic acid/bidistilled water and 0.1% formic acid/acetonitrile. The electrospray ionization source worked in positive ion mode and the mass spectrometer operated in selected reaction monitoring mode. Our bioanalytical method was successfully validated according to the FDA-EMA guidelines on bioanalytical method validation. The calibration curves resulted linear (R2 ≥0.9948) over the concentration ranges (1–10000 ng/mL for paclitaxel and 1–1000 ng/mL for 6α-hydroxy-paclitaxel) and were characterized by a good accuracy and precision. The intra- and inter-day precision and accuracy were determined on three quality control concentrations for paclitaxel and 6α-hydroxy-paclitaxel and resulted respectively <9.9% and within 91.1–114.8%. In addition, to further verify the assay reproducibility, we tested this method by re-analysing the incurred samples. This bioanalytical method was employed with success to a genotype-guided phase Ib study of weekly paclitaxel in ovarian cancer patients treated with a wide range of drug's dosages.[9]

10. HeLian et.al reported UPLC-MS/MS method for simultaneous quantification of Paclitaxel with the title "A rapid and sensitive determination of paclitaxel in rat plasma by UPLC-MS/MS method: Application to a pharmacokinetic study" is described as follows: A rapid and sensitive method for quantitative determination of paclitaxel in rat plasma was developed and validated by using ultra-performance liquid chromatography-tandem mass spectrometry (UPLC-MS/MS). Docetaxel was used as an internal standard and diethyl ether was the liquid–liquid extraction agent. Multiple reaction monitoring (MRM) mode via positive electrospray ionization (ESI) was applied to detect paclitaxel and IS at the transitions m/z 854 → 286 and m/z 808.48 → 527.3, respectively. This method covered a linearity range from 5 to 5000 ng/ml, with the total run time of 3.0 min. In summary, a high-throughout UPLC-MS/MS method was successfully developed to measure paclitaxel in rat plasma and was applied to pharmacokinetic study after intravenous administration of paclitaxel.[10]

11. Serena Mazzucchelli et.al reported LC-MS/MS method for simultaneous quantification of Doxorubicin with the title "LC-MS/MS method development for quantification of doxorubicin and its metabolite 13-hydroxy doxorubicin in mice biological matrices: Application to a pharmaco-delivery study" is described as follows: This study describes the development of simple, rapid and sensitive liquid chromatography tandem mass spectrometry method for the simultaneous analysis of doxorubicin and its major metabolite, doxorubicinol, in mouse plasma, urine and tissues. The calibration curves were linear over the range 5-250 ng/mL for doxorubicin and 1.25-25 ng/mL for doxorubicinol in plasma and tumor, over the range 25-500 ng/mL for doxorubicin and 1.25-25 ng/mL for doxorubicinol in liver and kidney, and over the range 25-1000 ng/mL for doxorubicin and doxorubicinol in urine. The study was validated, using quality control samples prepared in all different matrices, for accuracy, precision, linearity, selectivity, lower limit of quantification and recovery in accordance with the US Food & Drug Administration guidelines. The method was successfully applied in determining the pharmaco-distribution of doxorubicin and doxorubicinol after intravenously administration in tumor-bearing mice of drug, free or nano-formulated in ferritin nanoparticles or in liposomes. Obtained results demonstrate an effective different distribution and doxorubicin protection against metabolism linked to nano-formulation. This method, thanks to its validation in plasma and urine, could be a powerful tool for pharmaceutical research and therapeutic drug monitoring, which is a clinical approach currently used in the optimization of oncologic treatments.[11]

12. Medhat Al-Ghobashy et.al reported LC-MS/MS method for simultaneous quantification of Methotrexate, 6-mercaptopurine and 6-thioguanine nucleotide with the title "Development and validation of LC–MS/MS assay for the simultaneous determination of methotrexate, 6-mercaptopurine and its active metabolite 6-thioguanine in plasma of children with acute lymphoblastic leukemia: Correlation with genetic polymorphism" is described as follows: In this study, a specific, accurate and sensitive liquid chromatography tandem mass spectrometry (LC–MS/MS) has been developed for determination of methotrexate (MTX), 6-mercaptopurine (MP) and its metabolite 6-thioguanine nucleotide (TG) in human plasma. Based on the basic character of the studied compounds, solid phase extraction using a strong cation exchanger was found the optimum approach to achieve good extraction recovery. Chromatographic separation was carried out using RP-HPLC and isocratic elution by acetonitrile: 0.1% aqueous formic acid (85:15 v/v) with a flow rate of 0.8 mL/min at 40 °C. The detection was performed by tandem mass spectrometry in MRM mode via electrospray ionization source in positive ionization mode. Analysis was carried out within 1.0 min over a concentration range of 6.25–200.00 ng/mL for the studied analytes. Validation was carried out according to FDA guidelines for bioanalytical method validation and satisfactory results were obtained. The applicability of the assay for the monitoring of the MTX, MP and TG and subsequent application to personalized therapy was demonstrated in a clinical study on children with acute lymphoblastic leukemia. Results confirmed the need for implementation of reliable analysis tools for therapeutic dose adjustment.[12]

13. Lejing Lian et.al reported UHPLC-MS/MS method for simultaneous quantification of Methotrexate with the title "Development and Validation of UHPLC-MS/MS Assay for Therapeutic Drug Monitoring of High-dose Methotrexate in Children with Acute Lymphoblastic Leukemia" is described as follows: This report described a sensibility and validation of ultra-high performance liquid chromatography tandem mass spectrometry (UHPLC-MS/MS) method for therapeutic drug monitoring (TDM) of methotrexate concentration in children's plasma. One-step protein precipitation of samples was accomplished by adding 200 μL of acetonitrile to 100 μL of plasma sample. The separation of plasma samples was carried out on a ZORBAX Eclipse Plus C18 Rapid Resolution HD column with gradient elution using a mobile phase constituted of acetonitrile and 1% formic acid. The detection was executed by electrospray ionization (ESI) of triple quadrupole tandem mass spectrometer (TQMS) in the multiple reaction monitoring (MRM) mode with the transitions m/z 455.2 → 307.9 for methotrexate and m/z 458.2 → 311.2 for IS, separately. Linear concentration range of the calibration curve was 44–11,000 nmol/L and 44nmol/L was the lower limit of quantification. The methotrexate elution time was at 1.577 min, and the overall running time was only 3.3 min. The intra- and interday precision for all the analysis results was within 11.24%, and mean recoveries rate of methotrexate exceeded 87.98%. The described and fully validated UHPLC-MS/MS method was successfully applied in clinical TDM after infusion of high-dose methotrexate 1–5 g/m2 to 41 childpatients.[13]

14. Barbara Büchel et.al reported LC-MS/MS method for simultaneous quantification of 5-fluorouracil with the title "LC-MS/MS method for simultaneous analysis of uracil, 5, 6-dihydrouracil, 5-fluorouracil and 5-fluoro-5, 6-dihydrouracil in human plasma for therapeutic drug monitoring and toxicity prediction in cancer patients" is described as follows: Authors reported the development of a liquid chromatography-tandem mass spectrometry assay for simultaneous quantification of U, UH(2) , 5-FU and 5-FUH(2) in human plasma. Samples were prepared by liquid-liquid extraction with 10:1 ethyl acetate-2-propanol (v/v). The evaporated samples were reconstituted in 0.1% formic acid and 10 μL aliquots were injected into the HPLC system. Analyte separation was achieved on an Atlantis dC(18) column with a mobile phase consisting of 1.0 mm ammonium acetate, 0.5 mm formic acid and 3.3% methanol. Positively ionized analytes were detected by multiple reaction monitoring. The analytical response was linear in the range 0.01-10 μm for U, 0.1-10 μm for UH(2), 0.1-75 μm for 5-FU and 0.75-75 μm for 5-FUH(2), covering the expected concentration ranges in plasma. The method was validated following the FDA guidelines and applied to clinical samples obtained from ten 5-FU-treated colorectal cancer patients. The present method merges the analysis of 5-FU pharmacokinetics and DPD activity into a single assay representing a valuable tool to improve the efficacy and safety of 5-FU-based chemotherapy.[14]

15. Tormod Karlsen Bjånes et.al reported LC-MS/MS method for simultaneous quantification of Gemcitabine with the title "Preanalytical Stability of Gemcitabine and its Metabolite 2′, 2′-Difluoro-2′-Deoxyuridine in Whole Blood—Assessed by Liquid Chromatography Tandem Mass Spectrometry" is described as follows: Gemcitabine (2′,2′-difluoro-2′-deoxycytidine, dFdC) and metabolite (2′,2′-difluoro-2′-deoxyuridine, dFdU) quantification is warranted for individualized treatment strategies. Analyte stability is crucial for the validity of such quantification. Authors studied the impact of the time interval from blood sampling to separation of plasma on gemcitabine stability. Blood from gemcitabine-treated patients was drawn into tetrahydrouridine (THU)-spiked heparin and ethylenediaminetetraacetic acid tubes and kept on ice until separation. Plasma was separated sequentially up to 24 h after sampling and dFdC and dFdU were quantified by liquid chromatography tandem mass spectrometry (LC–MS/MS). The change in plasma concentrations over time was compared with the highest imprecision for concentrations above the lower limit of quantification of the LC–MS/MS method. Analyte concentrations decreased slightly over time, but for samples stored for 4h on ice, the decline was smaller than the expected analytical imprecision. After 24h, the maximum decline was 14.0%, which exceeded the expected analytical imprecision. dFdC and dFdU stabilities were acceptable for at least 4h when THU-spiked whole blood samples were kept on ice. This is within the scope of routine sampling procedures. Further, variations in separation time intervals within this time frame are negligible when interpreting drug concentrations.[15]

16. Yilin Sun et.al reported UFLC-MS/MS method for simultaneous quantification of Gemcitabine with the title "Simultaneous determination of gemcitabine prodrug, gemcitabine and its major metabolite 2', 2'-difluorodeoxyuridine in rat plasma by UFLC-MS/MS" is described as follows: To improve bioavailability and provide resistance to deamination, an array of gemcitabine (dFdC) prodrugs carrying the acyl modifications has been successful in the optimization of pharmacokinetic properties of dFdC, but the reports about 4-N-carbobenzoxy-dFdC (Cbz-dFdC), a dFdC prodrug bearing alkyloxycarbonyl modification, are relatively rare. Notably, in vivo enzymatic hydrolysis was an absolutely essential factor for the activation of these prodrugs, which is correlated with the anti-tumor activity. Therefore, detailed metabolism studies of Cbz-dFdC should be carried out for a more authentic pharmacodynamic evaluation. In order to detect the pharmacokinetic characteristics of Cbz-dFdC, a selective, sensitive and accurate method for the simultaneous determination of Cbz-dFdC, along with dFdC and its major metabolite dFdU in rat plasma was developed and validated using UFLC-MS/MS

techniques. Column was at 40 °C for separation using an eluent with acetonitrile and 0.1% formic acid, 1 mM ammonium formate at a flow rate of 0.2 mL/min. Detection was performed using ESI source in positive ion selected reaction monitoring mode by monitoring the following ion transitions m/z 398.1 → 202.2 (Cbz-dFdC), m/z 264.1 → 112.0 (dFdC), m/z 265.3 → 113.2 (dFdU) and m/z 246.1 → 112.0 (IS). Analytes were extracted by simple precipitation with acetonitrile containing internal standards followed by liquid-liquid extraction with ethyl acetate. The calibration curves of Cbz-dFdC, dFdC and dFdU were linear in the concentration range of 2 to 500 ng/mL, 2 to 500 ng/mL and 40 to 10,000 ng/mL, respectively. The assay ranges selected for the three analytes were appropriate and minimized the need for reanalysis. All the validation data, such as intra- and inter-day precision, accuracy, selectivity and stability, were within the required limits. In conclusion, the sensitive analytical assay was selective and accurate for the determination of rat plasma concentrations of Cbz-dFdC, dFdC and dFdU from a single LC-MS/MS analysis and well-suited to support pharmacokinetic studies.[16]

S. No.	DRUGS	HYPHEN-ATED METHOD	SAMPLE PREPARA-TION METHOD	SAMP-LE TYPE	ANALYTICAL PARAMETER
1.	Cyclophosphamide and Doxorubicin	LC-MS/MS	Protein precipitation	Human plasma	Relative Error & Relative Standard Deviation.
2.	Cyclophosphamide and Ifosphamide	GC-MS	Liquid-liquid extraction	Human urine	The Limit Of Detection & Signal-To-Noise Ratio.
3.	Melphalan	LC-MS/MS	Protein precipitation & Solid phase extraction	Human plasma	Precision & Accuracy.
4.	Laromustine	LC-MS/MS	Liquid–liquid extraction	Human plasma	Selectivity, Limit Of Quantitation, Linearity, Precision, Accuracy, Recovery, Autosampler Viability, Retention Time, Freeze–Thaw Cycles and Compounds Stability.
5.	Vincristine	LC-MS/MS	Protein precipitation	Human plasma	The Limit Of Quantification, Precision, Accuracy, Intra-Day Precision And Accuracy, Inter-Assay Precision and Accuracy.
6.	Vincristine	LC-MS/MS	On-line solid-phase extraction	Human plasma	Intra-Day And Inter-Day Assay Precision, Relative Standard Deviation and Mean Percentage Deviation.
7.	Vincristine	UPLC-MS/MS	Liquid–liquid extraction	Human plasma	The Lower Limit Of Quantification, Precision, Relative Standard Deviation, Accuracy and Relative Error
8.	Paclitaxel	LC-MS/MS	Protein precipitation	Human plasma	Precision & Accuracy
9.	Paclitaxel	LC-MS/MS	Protein precipitation	Human plasma	The intra- and inter-day Precision and Accuracy.
10.	Paclitaxel	UPLC-MS/MS	Liquid–liquid extraction	Rat plasma	Linearity range
11.	Doxorubicin	LC-MS/MS	Protein precipitation	Mouse plasma, urine and tissues.	Accuracy, Precision, Linearity, Selectivity, Lower Limit Of Quantification and Recovery.
12.	Methotrexate,6-mercaptopurine and 6-thioguanine nucleotide	LC-MS/MS	Solid phase extraction	Human plasma	Bioanalytical Method Validation
13.	Methotrexate	UHPLC-MS/MS	Protein precipitation	Human plasma	Limit Of Quantification & The intra-day and inter-day Precision.
14.	5-fluorouracil	LC-MS/MS	Liquid-liquid extraction	Human plasma	Range
15.	Gemcitabine	LC-MS/MS	Protein precipitation	Human plasma	Limit Of Quantification
16.	Gemcitabine	UFLC-MS/MS	Liquid-liquid extraction	Rat plasma	Intra- And Inter-Day Precision, Accuracy, Selectivity and Stability.

CONCLUSION

This paper describes critical view of bio analytical method used for qualitative and quantitative estimation of anti-cancer molecules with hyphenated techniques. Authors of this paper tried to compile the authenticated data available from standard data bases of Scopus and Web of Sciences. Critical Parameters for this review include type of cancer, diagnosis, treatment and qualitative and quantitative estimation in bio samples for therapeutic drug monitoring. In qualitative and quantitative analysis, various critical parameters considered are separation techniques that are protein precipitation, solid phase extraction, liquid liquid extraction and the column, detector along with various validation parameters.

CONFLICT OF INTEREST

The authors report no conflicts of interest in this work.

ACKNOWLEDGMENT

Authors are thankful to Sultan-Ul-Uloom College of Pharmacy, Banjara hills, Hyderabad for providing laboratory research facilities.

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