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The Role of Analytical Chemistry in Modern Drug Development

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Abstract: Analytical chemistry-the broad field of chemical research dedicated to the measurement and identification of substances deliberated or unwanted at a certain place and a certain time, underlies a great extent of all developments in chemistry. But unfortunately, analytical work as a somehow poor sister is not noticed by the public as much as important discoveries and new products get all the attention. Although it is not a new phenomenon, the verdict of analytical chemistry as a scientific Cinderella gained more evidence in the last decades with the advent of concoctions such as high throughput assay, system biology or combinatorial chemistry. While this is true, it is quite wrong that research results from top analytical labs largely influence the product pipeline in the pharmaceutical industry and also play a key role when it comes to process optimization and failure analysis. Potency assays for still regulated pharmaceuticals like digitalis; diagnostic test kits for parameters such as blood glucose, cholesterol or vitamin D 3; the role of technically sophisticated instruments, it is

not at all appropriate to view analytical chemistry as a mere ‘service discipline.

Introduction to Analytical Chemistry in Drug Development

Analytical Chemistry has been regarded as a core discipline of Chemistry for a long time. Up until 1960 these were a lot of Analytical Chemistry Institutes, sometimes combined with Biochemistry, in the former GDR and also in Czechoslovakia and parts of the former Soviet Union laboratories. However, in the course of the “Neuem Steuerungsmodell,” which had much more impact than just in the public service, most of these Analytical Chemistry Institutes were shut down by the regulatory authorities. Consequently, for a time, a lot of Analytical Chemistry experts – now without an “own” chemical discipline anymore – were called “Türsteher der Chemie” (chemistry bouncers!), since nowadays food, water and even body fluids (biomedical analytics) can frequently not be checked by their “Guardians” any more [3]. For a long period of time Analytical Chemistry was seen by many as a rather “unclean” discipline and not as a “real” part of Chemistry. Indeed, although having its own cutting edge developments during these times, analytical chemistry long has profited much more than most other fields of chemistry from advances in other areas. Concerning the topic of this symposium, Analytical Chemistry was usually not seen as an own discipline but as part of inorganic, organic or biochemistry. Now that all people are getting more aware of its importance, it becomes more important for AC too to stronger emphasize this importance and also its independence from inorganic, organic or biochemistry. This paper wants to at least give a few “hard” facts about AC. The well-founded insight of the enormous significance and the still unsatisfactorily exploited potential of AC should lead to demand a political reshuffle and not to the elimination of the existing Analytical Chemistry Institutes and thus prevent a neglect of the field that might have serious consequences. [4][5]

2. Fundamental Principles of Analytical Chemistry

Analytical Chemistry is defined as the “science and the art of determining the composition of materials in terms of the elements or compounds contained”. This essential branch of chemistry is practiced in virtually all laboratories that carry out chemical research. Analytical method is defined as a specific application of an analytical technique to solve an analytical problem. Analytical Methods is also defined as the consideration of chemical analytical techniques and procedures, based upon an understanding of the fundamental principles of the chemistry involved, to meet the scientific requirements of the analysis [6]. The design of an analytical method is the description of how to proceed to perform the analysis. In analytical chemistry, it is important to gain detailed information about the qualitative and quantitative composition of substances and chemical species. A crucial area in pharmaceutical and other research is the development of new drugs. Such endeavor is often termed drug discovery. One particular chemist applies to this field of research is in the use of analytical techniques to provide detailed information about the chemical composition of a wide range of novel compounds. Knowledge of the chemical nature of these novel compounds may be used in attempts to define the mode of action of a particular drug and in clinical trials to ascertain the safety and efficacy [7][8][9].

In quantitative analysis the question being addressed frequently is simply: how much is present? Non-instrumental methods depend on fundamental chemical properties, such as mass, volume, concentration, weight percentage, shift in analytical signal, etc. Instrumental method is defined as equipment used to generate measurement signals, which provide information regarding the chemical or physical sample is to be analyzed. Instrumental method is an exciting and fascinating part of chemical analysis that interacts with all areas of chemistry and with many other areas of pure and applied sciences [10]. In an increasingly complex and regulated world pharmaceutical and research institutions are turning more and more to sophisticated instrumental methods for the

acquisition of data. Analytical instrumentation plays a key role in the production and evaluation of new products and in the protection of consumers and the environment [11][12]. It is the instrumentation that provides lower detection limits required to assure the purity of foods, drugs, water, and air. It is the instrumental techniques that enable the development of new technologies through the reagent and catalyst that have provided breakthroughs in materials science, biology, and environmental science. This enables it to be applied to the entire characterization of a sample. Analytical chemistry now relies heavily on the use of electronic devices, which, through the use of computer systems, have significantly increased the speed and accuracy of the analysis of the samples. Most importantly, the instrument provides a wealth of pertinent information about the nature of the chemical species in a given sample. Broadly speaking most instrumental techniques fit into one of the following four principle areas: spectrophotometric techniques, electrochemical techniques, physical methods of chemical analysis, chromatographic techniques. [13][14][15]

2.1. Separation Techniques

An analytical chemist is the first line of defense in the development of a drug, as he or she reports the physical and chemical properties of the compounds after analyzing. Traditionally, methods were restricted to the use of classical wet chemistry which was confirmed by chromatographic methods. Chromatography remains as the key player in the drug development process followed by other sophisticated techniques primarily mass spectroscopy which calls for an insightful view of these analytical techniques in current drug development scenario. The role of an analytical chemist in the pharmaceutical industry at various stages of drug development is detailed. With the changing role of the analytical chemist and the advances in analytical techniques, there is a big ‘boom’ in the analytical instrumentation with advanced software benefiting the drug development process. [16][17]

Separation is isolating analytes by eliminating interferences. Analytes are chemicals or species being analyzed [18]. Interferences are substances in the sample matrix that could adversely affect the analytical determination of analytes. Separation and detection are the key aspects of many modern analytical methods. Separation of components is the isolation of analytes, i.e., separating analytes from one another and/or from interferences. Most separation methods involve two separate steps: first, the separation of the analytes into distinct chemical species, and second, the detection or quantitative measurement of analytes. Instrumental methods, especially, may be used to separate samples prior to detection with high capability and selectivity. These methods include chromatography, electrophoresis, and field flow fractionation. A series of chemical and instrumental methods that allows the determination of concentration of any substance in drugs, it is not known what role is it playing in the healing. To make drug available in proper and useable form, physic-chemical analysis are carried out. Such form of drug is mostly used as a suspension, tablets, capsule etc. Formed drugs also have some standard to be used in proper way as well and the bioavailability and stability of a drug (drug storage) is to be justified. [19][20][21][22]

2.2. Spectroscopic Techniques

Spectroscopic techniques play an important role in the pharmaceutical industry. They are widely used to characterize either pharmaceutical products (quantification of the API, assay of e.g. impurities/polymorphs/crystal forms, chiral discrimination) or the processes involved in the manufacturing of said products (end-process control, determination of the critical process parameters). The widespread success of the spectroscopic methods is mainly due to their desirable characteristics of being rapid, cheap, non-invasive/non-destructive, and also to their versatility, as they can be applied for a wide range of tasks, and are available both off-line (i.e. sample-treating in a laboratory, then measuring) and in-/at-/on-line (i.e. directly measuring the sample during the process). Spectroscopic techniques (in the broad sense) are based on different physical principles exploitable in the UV-vis, NIR, mid-IR, Raman, NMR, and Fluorescence ranges [23]. Whatever the specific technique, the continuous measurement of the samples results in spectra, chromatograms, or electropherograms (hereafter, profiles) carrying a high amount of information

on the system under analysis. Nonetheless, such rich raw data are unsuitable for straightforward interpretation. A significant aid in the extraction of useful knowledge from the profiles can profitably come from the application of a particular branch of mathematic and statistics devoted to the data analysis: chemometrics. This discipline encompasses a wide array of models and methods, most of which are multivariate, i.e. dealing with datasets where more than one variable is collected for each sample. Chemometrics can then be seen as a toolbox of approaches that can be exploited to better understand the sample characteristics. In this scenario, the goal is twofold: unsupervised exploration of the collected data in order to spot potential outliers, and (I) explanation and/or exploitation of the common variability, possibly through the identification of latent variables (e.g. Pr. Comp.), or through the investigation of the correlation structure between the spectral variables (e.g. Pr. Coor.). Alternatively, a priori knowledge concerning the samples can be used to build statistical models capable of predicting quantitative (calibration models, e.g. RM) or qualitative (classification models, e.g. SIMCA, B) responses. [24][25][26]

2.3. Chromatographic Techniques

Introduction

Analytical Chemistry is the study of the separation, identification, and quantification of the chemical components of natural and artificial materials. Analytical chemistry deals with the science of obtaining, processing, and communicating information about the composition and structure of matter. In a more practical sense, it is the assessment of how to analyze the materials that make up a given environment such as the concentration and/or structure of the analytes in contaminated soil. Analytical chemistry is itself broken down into several sub-disciplines that are used in such areas as drug analysis, food safety, forensic science, environmental studies, and quality control. Analytical chemistry is often involved in the synthesis and characterization of the materials associated with drug analysis and related engineering fields [18]. It is also often engaged with an understanding of the materials in terms of composition, deterioration, and textile applications. None of this, however, is direct forensic analysis of artifacts and other materials. Rather, it attempts to understand those processes and materials used in such activities. It is so broad an arena, both in theory and practice, that it is hard to capture in an easy definition. [27]

3. Analytical Techniques in Drug Discovery

Separations are key aspects of many modern analytical methods. Real world samples contain many analytes. Separation isolates analytes. Most separation methods involve separation of the analytes into distinct chemical species, followed by detection. Instrumental methods are widely used to separate samples using chromatography, electrophoresis or field flow fractionation. The separation power of these instrumental methods is generally expressed by the theoretical plate number N, which is proportional to the column length L and is inversely proportional to the variance of the peak at the half height σ2. The number of theoretical plates N under a column is directly proportional to retention time, and the constant C is the proportionality constant. Partition chromatography is based on the distribution of the solute between a mobile and a stationary phase. The distribution of the solute between two phases is described by the partition coefficient K. Therefore, potentiating the efficiency of this kind of techniques may improve the quality of the measurement. Analytical chemistry plays an important role in pharmaceutical analysis [18]. The efficiency of the chromatographic columns has been innovated in the last years allowing high throughput analyses at elevated resolutions with very small sample volume. These method developments prompted the search for efficient sample preparation methods. Although sample preparation seems to be a very simple, straightforward step, suggesting the formation of an identical sample, it is far from being simple. Therefore, the safeguarding of the analyte is the partitioning of the interfering species. Sample preparation also helps to protect expensive analytical equipment against degradation, and may permit to preconcentrate the analyte to make its detection more sensitive. The most widely used sample preparation techniques, their instrumental aspects, the critical variables affecting the performance of the method, and

combinations of the techniques with high performance liquid chromatography (HPLC) are discussed together with a broad review of the applications reported in the literature. Sample preparation methods have been rapidly developing in the last years, mostly due to advances in modem instrumental analytical techniques and developments in sample preparation technologies [28][29][30][31]. High performance liquid chromatography has become an important chromatographic technique for both the purification and the analytical investigation of a great variety of samples. Moreover, this technique generated widespread interest in sample preparation methods. The properties of real samples, such as the complexity, wide variation in sample matrix composition, or analyte concentration, necessarily often require that the biological or environmental sample be properly conditioned prior to HPLC analysis [10].

3.1. High-Performance Liquid Chromatography (HPLC)

Analytical chemistry has long been an integral part of drug development. The early stages of drug discovery are notable for materials that are analyzed; the final stages only conform to a particular compound following processing (formulation, tabletting etc.). A wide range of analytical techniques are at the disposal of the developers. For more than a century the medicinal chemist has had gravimetric methods, melting point determinations, TLC, titrations as well as GC and IR from the 1950s onwards. In recent years there has been an explosion in an array of new analytical techniques - NMR, SEM, ICP-MS, RAMAN, surface area analysis, SIMS and X-ray powder diffraction. [7][32][33][34] Due to its sensitivity, speed and ability to separate and quantify its components, liquid chromatograph has become the most popular techniques for the analysis of the major ingredients and the variety of impurities in such samples. In addition, in recent years, both improvements in the design of analytical chromatographs such as the introduction of GPC combined with a mass spectrometer NMR and preparative chromatography and the development of a host of new materials have substantially enhanced the power of the technique [35]. High performance liquid chromatography (HPLC) plays a very important role in quality control of pharmaceuticals.

3.2. Mass Spectrometry (MS)

Mass Spectrometry (MS) The high selectivity and sensitivity of mass spectrometry techniques make them particularly valuable for the determination of drugs and metabolites in various matrices. Mass spectrometry is used to construct the molecular profiles of the individual analytes and is being accepted as the final confirmation technique for parent drugs and metabolites in the presence of isobaric components that cannot be separated. Massive improvements in analytical flow rates and double-stage mass spectrometry have further raised the performance demands on their interfaces with the other chromatographic components of the system. There are a number of interfaces that have found acceptance for LC/MS. The sensitivity of MS means that further elaboration in terms of building up molecular mass fragments can be used for structural elucidation, especially when deuterium isotope-labeled analogs are used [36][37]. Various other mass spectrometric methods are also necessary to establish structural identity for metabolites and confirm the authenticity of their retention time diagrams by comparison of their MS behavior and fragmentation products with those of synthetic analogues. Ionization methods, which are used in order to transfer the solutes into the gas phase, apply either fragmentation mechanisms or the use of reagents from the liquid phase. Only the methods that do not influence or interfere with the chromatographic resolution of the separation are suitable for GLC and HPLC. The various MS approaches and tandem mass spectrometric techniques have developed into the most reliable way of identifying low levels of the compounds, in comparison to UV and other end detectors in HPLC and GLC analyses. Data systems can provide extensive library searching and retention index matching against large resident liquid chromatography data files [1][2]

3.3. Nuclear Magnetic Resonance (NMR)

The importance of NMR in the fight against neglected diseases is briefly evaluated. The antimalarial activity of metal compounds is used to illustrate the potential of stable isotope NMR

to discern the pathways of unrelated biochemical processes in intact micro-organisms. It can be used therapeutically, as an iron carrier in Fe-limited bloodstream, or to facilitate passive drug transfer. Careful screening of metal-based antimalarials gives pyridyl-allozone dicarboxamide 1, a promising drug; as clinically evaluated in vivo it yields small molecule pathology profile 2. From the EPR traces, 1 is observed to facilitate electron transfer between hematin and NADPH. Neither active nor passive metal redox cycling can be established [38]. Nuclear magnetic resonance (NMR) has been used to follow the fate of pharmaceutics formulated from a proprietary glyceride matrix, after oral and intravenous administration to male SpragueDawley rats. The absorption into the systemic circulation of LNM was observed irrespective of route. A series of fat-soluble marker compounds were co-administered both orally and intravenously to investigate the effect of LNM formulation on changes in absorption, distribution and metabolic processes in organs and tissues. Only one fat-soluble marker was metabolised to a significant extent in the livers of all treated groups, while other FAT suffered reduced metabolism after i.v. administration due to LNM induced hypo-perfusion. Metabolism of the fat-soluble test compounds in the liver appears to be an important factor in the pharmacokinetic characteristic of the compounds, which is influenced by route of administration and composition of the pharmaceutical formulation [39].

4. Quality Control and Assurance in Drug Development

Drug substances manufactured on an industrial scale must meet standards set for their Identity, Purity, Safety and Efficacy. Drug analysis in any step or at any stage of drug development or manufacturing, which includes route synthesis or extraction of raw materials, determination of purity of raw materials, intermediate products, end products, stability tests and assay of marketed formulations falls under the domain of analytical chemistry [40]. The modern trend in drug analysis is to use improved sophisticated instruments for handling samples and automation with least manual handling. The control action based on drug analysis can be classified as two categories: Time-based control, which is control action on critical process parameters; and Quality based control, which decides after recording the quality of the final output. Over the years the role of analytical chemistry has broadened to include: To screen drugs to monitor or define mass production of pharmaceutical products; On shelf products surveillance programs are necessary to ensure product stability and safety; Rigorous inspections for import and export of drugs; Quality control requirements for new chemical entities in a final dosage product are developed; Additional control may result as bulk drug manufactures or samples intermediates as part of their manufacturing processes or as trading control of bulk materials or products; and Impurity levels in finished products have to be determined and the validity of the analytical methods is essential [41]. In bulk drugs, precursor chemicals of API at its final stage of synthesis, the impurities are needed to control by an analytical report. The role of government/regulatory agencies is vital in the entire drug regulatory affairs for the safety and efficacy of the drug product for human use. [42]

Materials and Discussion

4.1. Method Validation

The validation process of analytical methods is in the spectrum of analytical studies concerning method validation of licensed medicines and may include API analysis, chemical testing or bioassay including bioHarborough and PK. Validation data collected like stability or process validation batches should be used for validation purposes if applicable. Analytical methods are developed in research & development and transferred into standardized lab procedures established for the quality control of finished drug products. The process validation guidelines require revalidation whenever changes are made in packaging, formulation, equipment or processes. The conditions under which the need for revalidation should be studied and documented include the following. (1) A change is made in a critical component of the commercial drug product, the API, or the primary packaging component. (2) Replacement of a critical piece of equipment. (3) Transfer of a process to a different facility. Another example is a significant increase or decrease

in the batch size of the drug product, API or intermediate [43][44]. In addition, a trend analysis could indicate that there is a particular problem (e.g., analytical method, or capability of a process). The problems mentioned above are a few of the examples that may indicate the need for revalidation of a drug product or process. Some higher-level benefits include increased throughput, reduction in rejections, and rework. Additionally, reduced testing could result. One contributing factor to the reduction of testing might involve identifying those parameters that have the greatest effect on the overall variability of the tested item and controlling these potential sources of variability. [7][44][45]

Results and Discussion

4.2. Impurity Profiling

On monitoring of the impurity purity, the term impurity is nowadays associated with the production process of some active pharmaceutical ingredient (API) or a drug product. In a broader sense, any organic or inorganic substance which is not intended to present in the standard pharmaceutical compound, is considered as an impurity. These might be, e.g. genotoxic substances in bulk substances, heavy metals, residual solvents or catalysts in the final single drug product. The International Conference on Harmonization of Technical Requirements for the Registration of Pharmaceuticals for Human Use (ICH) describes impurities in guidelines for residual solvents, in impurities: guideline for the safety qualifications and in impurity: guideline for the qualification of organic impurities [46].

A new generation of drug products as a highly sophisticated development has significantly improved patients' treatment. A drug of the new age is controlled by ARTIFICIAL INTELLIGENCE, and the presentation of it is not only the specific selection of active substances but also it is a functional combination of pharmaceutical excipients. The treatment enhancement underpins the personal touch to the therapy and it goes toward a patient-oriented dosage of drugs. In a new smart generation of drug products, everything should be rationally verified, including, e.g. the composition of the polymeric coating of the colon delivery mesalazine pellets. Normally, the local impurity control is the verification of the amount of odor, color and water in highly hygroscopic product during the production process. Ampicillin trihydrate features in the infrared spectra. [47][48][49]

4.3. Stability Testing

Chemicals are structurally modified until good results are obtained for biological activities and toxicity and they need to be classified and quantified in the final product. Other reagents, solvents, recipents that are used for synthesis of drug substance must be seperately measured as traces. Determination of levels of water is also important as most of the degradation products can only be formed in moisture of solvents. All of the determinations above must have high sensivity, selective, cheap cost and easy to apply and the main methods used for these determinations are spectrophotometry, chromatography and titrimetric methods. [50][51] Stability testing is the testing of the physical, chemical properties of product that changes over time. The changes could lead to decrease in efficacy, tissues or release in certain concentrations. The only way to get an idea of those characteristics is to obtain experimental data and examine the pattern of the medication or the drug substance reformed over time. Stability testing is an important part of the production of a new drug. The possible decomposition products must be determined in order to ensure that they are below a certain level and not pose any risks to human health; thar foray pharmaceutical must be analysed for the steps of raw matter to the final product [52]. This can only be achieved by using such analytically sensitive and selective, specifical analytical techniques such as HPLC, LC-MS. [53]

5. Analytical Techniques in Pharmacokinetics and Pharmacodynamics

Analytical Chemistry plays a vital role in the pharmaceutical development as well as in day-to-day analysis of drugs. Along with the discovery and synthesis of drugs, development (i.e. Tablet

formulation and its evaluation) and subsequent post marketing studies, the drug needs to be analyzed. There are plenty of chemical and instrumental methods that exist for the estimation of drugs. This review briefly describes various chemical methods usually found in pharmacies that can be used for drug analysis and more emphasis is given to the instrumentation and their corresponding methods that can be suitably employed for drug analysis [17][54]. Different analytical techniques and their corresponding methods with requirements of drug particles are subdivided into respectable physic-chemical properties are discussed. Apart from these, various aspects of importance from the chemical analysis are presented, like handling and storage of drug. Quality of pharmaceutical products, in general, depends on the environment controls during storage and its handling i.e. carton or container caps or curtain conditions, batches of drug, textile-fiber, rust or corrosion, control of storage area, controlled humidity, light contamination, storage and handling of different types of drugs in pharmacies. Characteristics of a perfect drug was stated as a drug should be 100% pure and effective towards the desired biological activity, should contain the label claimed active drug contents, it should possess the same pharmacokinetic profile batch by batch [18].

5.1. Bioavailability Studies

Bioanalytical methods are an important component of both preclinical and clinical aspects of drug development and for studies investigating residue levels used in food-producing animals. Bioanalytical methods must be subjected to validation by the interested parties, since they play a key role in the development and subsequent monitoring of drug usage and environmental safety. In addition to 'traditional' methods like microbiological techniques, enzyme-linked immunosorbent assay (ELISA), high performance liquid chromatography (HPLC) and capillary electrophoresis (CE), the fast developing biophotonics and mass-spectrometry-based techniques are also important group of the analytical methods. Integration of aptamers enables high sensitivity or shortened analysis time [57][58]. Genetically modified bacteria and peptides are novel tools suitable for the development of cheap, reliable and rapid microbiological screening methods of drug residues. Chemically modified immunoreagents are beneficial for the improvement of the selectivity and sensitivity of ELISA and HPLC methods. Microarray-based multiplex screening systems of antibiotic residue have a real possibility for commercialization [59]. At present low levels of drugs can be detected in complex matrices, like food of animal origin, the environment and human urine. Interpretation of the results generated by bioanalytical methods needs to be adapted to the investigated matrix and bioavailability of the compounds. Accurate data interpretation is particularly important for the registration of new veterinary drug products [60].

5.2. Drug Metabolism Studies

Analytical chemistry plays a significant role in drug development research to examine the chemical properties of potential drug candidates. During early drug discovery, researchers study the physiochemical properties of novel synthesized compounds which, on passing in-vivo pharmacokinetic tests, would better determine its drug-like potential. Furthermore, analytical chemistry aids the production of novel drug delivery systems and improves the standardization of the quality control of final medicines. In the next stages of medicine development like preclinical, clinical trials, and mass production, analytical chemistry is involved in drug metabolism studies, effectiveness, and safety evaluations, as well as in process control. Spectrophotometry, mass spectrometry (MS), liquid chromatography (LC) are just a few widespread analytical methods used in the fields of pharmaceutical research. Furthermore, studies combining spectroscopy, chromatography, and other techniques in one analysis system are becoming very advantageous. [61][62]

Drug metabolism is a crucial physiological process which occurs mainly in the liver. During drug metabolism, or xenobiotic metabolism, exogenous compounds are broken down (biotransformed) into metabolites that are eventually excreted from the human body via urine or bile. The metabolism of drugs is divided into at least two major routes of phase I and phase II metabolic

reactions [63]. When a drug is metabolized by drug-metabolizing enzymes, it is considered a parent drug, while the emerging formed metabolites are called drug metabolites. The significance of drug metabolism in the practice of drug development is dominantly related to the subsequent excretion of drug compounds. During in-vitro and in-vivo experiments with a drug molecule, a significant focus should be made in monitoring generated metabolites as they could potentially have toxic effects on the human body. The metabolic route of phase I and/or phase II reactions induces structural alterations to the substrate (drug), leading to the production of active metabolites, inactive metabolites and/or reactive metabolites. During in-vitro metabolism studies, if hepatocytes, liver microsomes or S9 fractions are used, these toxic and unexpected effects could be seen when structurally unsafe substrates are biotransformed and generate reactive metabolites. The formation of permanent covalent binding and/or OH• groups is common in hepatocyte NADPH assays [64][65][66][67]. Also, the electrode array allows the construction of semi-thin layer films that enhance the intense generation filtration of a specific metabolite. In the drug discovery and design process, in-vitro metabolic studies occur in the latest stages, aiming to: 1) monitor top drug compounds as metabolites, 2) compare candidate drug structures as the reactivity of the metabolism, and assess the associated biotransformation rate, and 3) evaluate hepatotoxicity, affiliated to the formation of drug-induced toxic metabolites. [68][17]

5.3. Pharmacokinetic Modeling

Pharmacokinetic modeling is probably implemented in the latest phase of drug discovery and development. Nonetheless, its potential has been widely exploited as an activity carried out by analytical chemists. New compounds discovered by the pharmaceutical industry need packaging and vehicle to be easily handled and to include the proper delivery dosage form. These packaging materials also have to be non-toxic and non-soluble for which methods are developed to follow the materials' quantification [69].

A very significant step after the first screening of bioactive compounds found in plants and other natural sources is the evaluation of the toxicological and pharmacological behavior as a compound to be used in new drug preparations. Besides to follow the material and its cognates of interest, it is also necessary to monitor the toxic metabolites of the active compound. LC-MS based methods were developed to follow these toxic compounds in the living essentials. Five different volatile compounds have been studied in the work ahead. It is intended to synthesize molecularly imprinted polymers (MIPs) as solid phase extraction material (SPE) for the preconcentration of these compounds and analyze these extracts by utilization of high performance liquid chromatography and mass spectrometric detection for method development. [70][71]

Some pilot works were performed in the adopted method development. The main aim is to develop a procedure that allows reaching good selectivity and sensitivity to analyze the compounds of interest in manner to be used to determine their amount leaching from the plastic container to the solution they contain. Method development for Cyclosporin and its cognates using immunosuppressive agent Sirolimus and in vivo pharmacokinetic analysis by use of high performance liquid chromatography-mass spectrometry for these compounds are described which is a complete process of analytical method development from its chemical derivatization to the in vivo administration and determination in blood and for every stage, these analytical methodologies were validated, a fundamental step regarding reliable quantitative analysis is concerned.

6. Analytical Techniques in Formulation Development

Over the course of drug development, analytical techniques are widely used as enabling and supporting technologies. The pharmaceutical industry, instrumental analysis, is required to prove the safety, efficacy, and stability of the drug. Various regulatory guidelines have recommended the use of analytical chemistry to characterize and quantify the compounds under study. Analytical techniques can be categorized as bulk or surface techniques based on characteristics. The drug development process is a complex procedure that involves various disciplines of science, such as chemistry, biology, pharmacology, and medicine. The main categories of pharmaceutical drug

development include preformulation studies, formulation development, pharmaceutical formulation, stability testing, and final formulation development. Pharmaceutical formulation development is the iterative process of combining different chemical components together with the active drug substance to produce a final drug product.

A dosage form is the structure in which the drug is administered to the subject, and it contains both active pharmaceutical ingredients (API) and inert substances (excipients). There are different types of pharmaceutical dosage forms including solid, semisolid, liquid, and parenteral formulations. The main objective of new drug development is to possess an optimized drug delivery system capable of delivering the drug in the right place with the right amount, at the right time with minimum toxic effects, cost-effectively, and with maximum patient compliance. In order to become a final marketed drug, one must undergo a rigorous, time-consuming, and multi-step trial during the drug development process. Formulation development starts with the screening of an optimized delivery system for effective drug delivery. The final drug dose might contain marginally active and inactive ingredients. It includes optimizing the selection of a drug delivery system, manufacturing scale-up and technology transfer, and the production of batches for clinical trials and marketing. The drug use process may be a solid dose form due to the improvement of the diffusion and dissolution rate [72].

6.1. Excipient Compatibility Studies

Analyzing the potential interactions of active pharmaceutical ingredients (APIs) with excipients is a regulatory requirement in the development of a pharmaceutical product. Nevertheless, this is a big challenge in the global market. Many vendors provide excipients that are not well characterized. In addition, many drugs are composed of very complex formulations which makes it very difficult to evaluate the compatibility of all respective ingredients. On the other hand, patents usually do not provide information on excipient compatibility studies [73].

6.2. Dissolution Testing

Dissolution testing is the first step in the process. It is conducted to evaluate evenness in product makeup and measure the time it takes for a tablet to fully dissolve [74]. Analyzing the dissolution performance of a stomach remedy in the United States Pharmacopeia Apparatus 2 and in a purpose-built minivessel dissolution system. The main goals are to compare both setups with a 6 times smaller volume at 500ml (full media vessel), whilst striving to model sink conditions for aspirin due to its high solubility, and in the course determine the efficiency characteristics of the minivessel setup. It discusses a number of challenges related to improving apparatus design and method development for such setups, including initial validation results for the minivessel system. Analysis is conducted of the concentration-time profiles of the Red Dye No.3 marker in USP Apparatus 2 and in a minivessel apparatus. Three types of tablet products are investigated: generic enteric-coated aspirin, buffered aspirin & enteric-coated products. Planned assessment involves granularities of ±10%, ±5%, and ±3%. [75][76]

6.3. Particle Size Analysis

Particle size analysis has an important role in the design, development, and production of drug products. In the pharmaceutical industry, a scientist encounters a large variety of chemicals differing in chemical and physical properties. Therefore, it becomes essential to employ appropriate safeguards to ensure that pharmaceutical products are of the desired quality. For this purpose, the physical characteristics of pharmaceutical particles are crucial for obtaining a safe and effective drug product. These characteristics influence: handling of materials; flow properties; setting up of formulations during product development; manufacturing process design; product performance, such as stability, release, and bioavailability; the in-vivo dissolution rate and bioavailability; stability or cake formation in the vial or infusion bags after reconstitution; and in-vivo behaviour, like phagocytosis of drug delivery nanoparticles. The decision on concentration range for conducting the method verification depends upon the nature of the analyte and the type

of the method being validated. In this case, the concentration range of the verification standard was chosen in such a way that three values of the verified drug substance specification could be approached simultaneously. [77][78][79] The calibration, robustness, and reproducibility need to be assessed as a usual system validation. It is always recommend a particular sample to be characterized by at least two different techniques to develop a cross-correlation and thus obtain a better idea about the particle properties of the sample [80]. As pharmaceutical industries are considered, almost every company has a particle size method in susceptible interest. Therefore, further development in the design and technology of particle size characterization instruments can be anticipated in the near future. Here the dispersion methods used for particle size characterization are diagnosed and it is stated that they need to be revised and modified. Newer and better computer software needs to be developed that would enable computer analysis of the acquired data and compound and equivalent particle diameter calculation. To cope with many applications, this would have to work on-line, being at the same time connected with the particle size analyzer. Nowadays, scientists prefer to describe the whole particle size distribution range instead of just mentioning a single value. Nevertheless, sources of possible errors associated with instruments have to be looked into and mentioned in the final specifications [81].

7. Emerging Trends in Analytical Chemistry for Drug Development

In the face of rapidly progressing instrumental developments, modern analytical chemistry continues to provide innovative solutions for tomorrow's challenges. Despite the effort to save resources and to speed up analytical procedures, the sensitivity of the methods used must be constantly improved due to decreasing trace concentrations of the analytes of interest. The issue becomes even more critical in the context of the analysis of complex biological matrices. Particularly in the case of drug metabolism, structural elucidation and pharmacokinetic/pharmacodynamic studies, low abundance analytes must be often detected and quantitated. This implies a thorough and highly selective sample preparation of the biological specimen. The sample treatment may be a long and tricky step that can introduce potential errors at any stage of the analysis. For this reason, miniaturized and automated techniques are increasingly being applied in clinical and pharmaceutical analysis. Standard and novel procedures for the extraction and chromatographic separation of analytes are reviewed together with specific examples of applications for the assay of drugs in human or animal plasma and urine. At the same time, the latest and most promising developments are also discussed, such as: pressurized liquid extraction, restricted access materials, solid-phase microextraction, and coupled techniques involving the use of mass spectrometric detection. These techniques are able to overcome many of the limitations of classical procedures in terms of speed of analysis simplification and cost of the procedures [3].

7.1. Miniaturization and Microfluidics

Contemporary developments in handling and re-coding even more DNA, and soon cDNA, or part thereof, and proteins, require miniaturization of the wise man's tools. Behind the steady scientific theories, there is an even steeper progress, like the Angkor Wat style temples in Khmer, which has a tendency to generate cataclysms of floods, of information, without safety valve as in the case of the latter civilization. This is the reason analytical chemists try to follow the revolution through topoi like miniaturization, new detectors with new generations, and multimodal instruments (between 2 and 10), as well as new philosophical questions leading to epistomé optimization of one's. Large numbers of automata (if possible "intelligent") assisted problem solving (at the moment pattern recognition), and knowledge management by the end of the decade of two dozens of fields and relations [82]. It is time to invest in informational chemometrics! On the other hand, something of a panorama has been sketched over an original portion of the discipline, the history of analytical chemistry and at least its ultratrace portion, with both Hegelian patterns in terms of dyads. This historical approach could be seen as unduly partial, but it is probable that it contains some lessons and strategies towards the coming millenium. Indeed, history is much more predictive than univariate models. Additionally, a recurrent theme has been the research organism

itself of the author. Shall we take care of the experiments? Is there a second life for scientific dead-ends? So there are not only individual but a least family-type representations within the discipline [83].

7.2. High-Throughput Screening

High-Throughput Screening (HTS) is an approach to drug discovery that has gained widespread popularity over the last 20 years and has therefore become a standard method for drug discovery in the pharmaceutical industry. High-throughput screening is the process by which libraries of thousands of compounds are tested quickly and cost effectively for bioactivity. It is a process of screening and assaying a large number of biological modulators against a selected set of targets. These assays are employed for screening various types of libraries such as compound, genomic, RNAi, combinatorial chemistry, and spectroscopy. While the main goal of High-Throughput Screening is to accelerate drug discovery by screening large compound libraries, the rate may exceed a few thousand compounds per day. High-throughput screening (HS) processes are also increasingly used to characterize pharmacokinetic and toxicological data about new hits and drugs. [84][85]

High-throughput screening consists of several steps: target identification, reagent preparation, compound management, assay development, high-throughput library screening, data analysis, and compound validation. Considering that the majority of known dysfunctions do not have a direct etiology, it is not surprising, that the effective nature of High-Throughput Screening done to identify target? specific compounds is characterized by a precise, focused on a single mechanism treatment. Microreaction wells in tightly controlled, parallel arrangements composed of various materials have proven to be optimal for HTS. Initially, 96-well format plates were used, but this format is now being superseded by higher-density microplates. Presently, 384-well format plates are widely used, and companies are starting to use 1,536-well format or 3,456-well format microplates. In this arrangement, up to 10,000 compound screens can be performed per day. The development of new commercially available technologies will result in the widespread use of 15,360-well format plates, and therefore it will be possible to perform up to 100,000 assays per day. Pharmacological screening is carried out in three stages. In the first stage, the compounds are subjected to the primary screen; if a given compound gives a positive result or “HIT”, it is tested again in the second, secondary screen using a more sensitive and precise method. In the third stage, the hit is confirmed and analog compounds are assayed [86].

8. Regulatory Requirements and Compliance in Analytical Chemistry

Pharmaceutical regulatory agencies strictly enforce quality, safety, efficacy, and trade standards to protect public health. This influential factor places tremendous pressure on drug developers and manufacturers to attain regulatory compliance. As a result, the pharmaceutical industry is among the most regulated industries in the world. To market their drugs, companies must first obtain regulatory approval, and before that can happen, evidence of both safety and efficacy must be provided. Regulatory approval is contingent upon the submission of high-quality data generated by validated analytical methods, supporting not only safety and efficacy, but uniform quality as well. In order to ensure the safety and effectiveness of the marketed drug products, regulatory agencies require companies to adhere to Good Manufacturing Practice (GMP) standards. Consequently, this has burgeoned a growing need for GMP-compliant analytical methods and analytical departments. The term “regulatory science” falls under the umbrella of the highly interdisciplinary field of analytic science, which is responsible for developing and/or interpreting methods that measure drug substances, drug products, impurities, or manufacturing processes [10].

8.1. Good Laboratory Practices (GLP)

An objective/measurable and multifunctional dosing system, a quality conscious, well-documented process, or any combination of the above may well serve to characterize the GLP-

status of a method or system. Such a general classification is prior to provide some precision in the concept of "validation" as a method or system to be employed in a study compliant with GLP; as the concept of "validation" applies both to the programming system and to the methods once in use. [87][88]

8.2. Good Manufacturing Practices (GMP)

8.2.1. Historical Background Proper manufacturing of medicinal products or vaccines requires the establishment of detailed specifications in the form of a master formula. For all raw materials, this document should contain pharmacopoeial standards, and a complete description of production steps, equipment materials, and packaging, monitoring and verification procedures should be described. The implementation of this formula lays the groundwork for the development of modern GMP, which is increasingly important when biological materials are produced, which are far less standardized than most chemical raw materials. Manufacturing conducted according to GMP assumes that raw materials are of pharmaceutical quality, adequate facilities and equipment are suitable for the task, production is performed under clearly defined procedures, and all processing steps are extensively recorded and can be traced in case of any irregularity. Moreover, products must be retested to assess the quality and newly checked before distribution. Successful manufacture also implies the presence of staff who have received adequate training in the relevant procedures. Full documentation in the form of quality manuals or inner norms is also required. This so-called 'paper system' ensures an established quality of production [89].

9. Conclusion and Future Perspectives

In the fast changing environment of today specific issues and technologies will not be addressed in depth, as a risk runs of being outdated as soon as this background appears. The goal is instead to introduce a general view about analytical chemistry and to indicate the central position that it occupies, most notably the analysis of contaminants and relevant research fields. The final part of the manuscript deals with current needs, possible future trends and challenges. Particular but not exclusive emphasis is given to the way in which analytical chemistry is practiced in Austria at the Institute of Food Chemistry, the need for and design of laboratory facilities which will be opening in the near future, and current postgraduate activities and future plans. The former tend to scrutinise the scientific merits of research programmes and individual projects so that their technological implications are largely overlooked thereby resulting in naïve and unrealistic expectations on what may actually be delivered. Specifically, detailed results and the benefits of research are clearly missing from the files. By not dealing with issues, the absence of comments on time schedules and milestones, for example progress with the work plan or with the production of deliverables, deprives the whole of the expected propriety. The authors emphasize the importance of analytical chemistry, related disciplines and technologies, and the cooperation and communication between the different actors.

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