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CURRENT TRENDS IN MODERN PHARMACEUTICAL ANALYSIS FOR DRUG DISCOVERY

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Abstract:
Pharmaceutical analysis methods are traditionally and commonly applied to the chemical analysis of drug molecules. However, in the last two decades, modern pharmaceutical analysis has evolved enormously, capitalizing on hyphenation techniques, high-throughput technologies, chemometrics, and most recently miniaturization and nanotechnology. The combination of various techniques allows the modern pharmaceutical analyst to exploit the virtues of each technique and, in turn, to improve the overall quality of analysis with reduced cost, analysis time, and sample volumes.
High-throughput technologies are having an increasingly important role in early-stage drug development in the frame of preclinical and clinical ADME (Absorption, Distribution, Metabolism, Excretion) studies.chemometric methods applied in the domain of computer-aided drug discovery, and which prove particularly successful in early stage preclinical research as a fast computational and analytical tool for screening the increasing numbers of potential drug candidates.
Recently, the interest in miniaturization technology has grown rapidly, particularly in the pharmaceutical industry where it has been fuelled by the need to speed-up the analysis in high-throughput screening applications which focused on "lab-on-a-chip" nanotechnology because of the potential to identify, study, and evaluate new drug entities. Nanotechnology will have an increasingly important role in the development of commercial analytical and preparative tools.

Keywords: *Pharmaceutical analysis, Hyphenation techniques, High-throughput analysis, Chemometrics, Miniaturization, Nanotechnology.*

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INTRODUCTION:

The development of the pharmaceuticals brought a revolution in human health. These pharmaceuticals would serve their intent only if they are free from impurities and are administered in an appropriate amount. To make drugs serve their purpose various chemical and instrumental methods were developed at regular intervals which are involved in the estimation of drugs. These pharmaceuticals may develop impurities at various stages of their development, transportation and storage which makes the pharmaceutical risky to be administered thus they must be detected and quantitated. For this analytical instrumentation and methods play an important role in assessing the quality of the drugs.

Traditionally, pharmaceutical analysis referred to the chemical analysis of drug molecules. However, over the years, modern pharmaceutical analysis has evolved beyond this. They are

1. Hyphenated techniques,
2. High-throughput analysis,
3. Miniaturization,
4. Nanotechnology,
5. Microdosing studies, and
6. Chemometrics.

These analytical advances are now being employed in all stages of drug discovery and the focus of this will be on how these technologies are being employed within this process. With new, improved and evolving technologies, as well as new applications for existing technology, the search for new drugs for the prevention and treatment of human diseases continues.

1. HYPHENATED TECHNIQUES:

The hyphenated technique is developed from the coupling of a separation technique and an on-line spectroscopic detection technology. The remarkable improvements in hyphenated analytical methods over the last two decades have significantly broadened their applications in the analysis of biomaterials, especially natural products. recent advances in the applications of various hyphenated techniques, e.g., GC-MS, LC-MS, LC-FTIR, LC-NMR, CE-MS, etc.

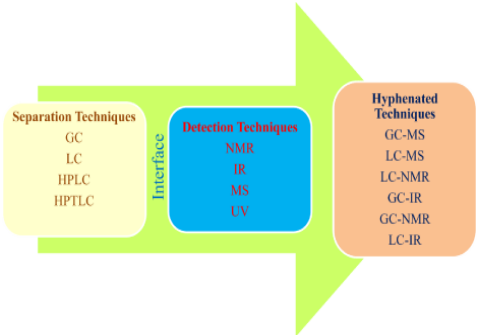

Figure.1: Hyphenated techniques

The determination of drugs in biological materials is an important step in drug discovery and drug development. Combination of techniques was first successfully accomplished with gas chromatography-MS (GC-MS) in the 1960s. By combining various techniques, the modern pharmaceutical analyst hopes to achieve the goal of pooling the virtues of each technique to establish purity and identity. Frequently this also permits the analysis of smaller sample volumes more quickly and provides more information content. Combining disparate techniques is frequently hampered by instrumental limitations. For MS, some of these limitations can be overcome by advances in ionization technology, such as electrospray ionization (ESI) and matrix-assisted laser desorption/ionization (MALDI) and the development of new probes.

HPLC together with various types of detection such as ultraviolet, fluorescence, and mass spectrometry has become the method of choice for bio analytical method development.Liquid chromatography electrospray ionization-mass spectrometry method for the qualitative and quantitative determination of metabolites.

APPLICATIONS:

- Combined HPLC–NMR spectroscopy is another rapidly growing technology, enabling the rapid and detailed structural characterization of complex mixtures.
- HPLC-NMR, as well as HPLC-NMR integrated with MS (HPLC-NMR-MS), have been applied to drug discovery, especially in the separation and structural elucidation of drug impurities, reaction mixtures, degradation products, in vitro and in vivo metabolites, and combinatorial library samples.
- NMR coupled with other analytical techniques has the intrinsic advantage of providing structural and dynamic details derived from NMR, as well as the high resolution and sensitivity provided by the other coupled techniques.

IMPORTANCE:

In the context of pre-isolation analyses of crude extracts or fraction from various natural sources, isolation and on-line detection of natural products, chemotaxonomic studies, chemical finger printing, quality control of herbal products, dereplication of natural products, and metabolomic studies are discussed.

2. HIGH-THROUGHPUT ANALYSIS:

High-throughput analysis (HTA) is methodology aimed at the rapid analysis of large numbers of

compounds. This field has been expedited by the requirement to provide analytical support for multiple drug targets emerging from the field of molecular biology, human genetics and functional genomics. Further drivers for development have been in the support for the analysis of large compound libraries arising from parallel and combinatorial chemistry, as well as economic pressure to reduce time-to-market for new drug molecules.

The ability to characterize and analyze large numbers of compounds in a high-throughput mode has thus become an integral component of modern drug discovery over the past decade.

HTA is having an increasingly important role in early stage drug development, providing qualitative and quantitative characterization of compound libraries and bio analytical support for preclinical and clinical ADME studies. This facilitates early elimination of unsuitable compounds, which could reduce the attrition rates of drugs later in clinical development, hopefully reducing development costs-currently estimated at US$800 million and time.

APPLICATIONS:

- HTA techniques currently support three main areas:
- Structural,
- Purity, and
- Quantitative determination.
- The current trend is to continually interpose automated techniques, in particular combination techniques, for HTA applications. Summarizes some of the current analytical techniques being applied in the pharmaceutical industry for HTA.

3. MINIATURIZATION:

One of the current trends of modern analytical chemistry is the miniaturization of the various tools daily used by a large number of researchers. Ultrafast separations, consumption of small amounts of both samples and reagents as well as a high sensitivity and automation are some of the most important goals desired to be achieved. For many years a large number of research laboratories and analytical instrument manufacturing companies have been investing their efforts in this field, which includes miniaturized extraction materials, sample pre-treatment procedures and separation techniques. Among the separation techniques, capillary electro migration methods (which also include CEC), microchip and nano-LC/capillary LC have received special attention. Besides their well-known advantages over other separation tools, the role of these miniaturized techniques in food analysis is still probably in an early stage.

APPLICATIONS:

- Applications in this field carried out by CEC, microchip, nano-LC and capillary LC are only a few when compared with other more established procedures such as conventional GC or HPLC.
- The scope of this is to gather and discuss the different applications of such miniaturized techniques in this field. Concerning CE, microchip-CE and CEC works.

4. NANOTECHNOLOGY:

In the broadest sense, nanotechnology is defined as products, processes and systems operating at Nano metric tolerance with dimensions of less than ~1,000 nanometers. The nanoworld is also associated with objects with dimensional limits of 100-300 nm. The US National Science Foundation projected that the total worldwide market size for nanotechnology will reach >US$1 trillion annually by 2015.

In drug discovery, advances in nanotechnology are accelerating the identification and evaluation of new drug entities. Currently, it is being employed in various fields of pharmaceutical analysis.New analytical tools using nanostructures that are sensitive enough to detect individual molecules have been developed. Individual chemical species can now be detected and manipulated using nanodevices, nanoprobes and nanobiosensors. Integration of functional aspects of biological and non-biological systems has resulted in the development of specialized systems such as nanobiosensors. Enzymes, antibodies, receptors and also their molecular imprints have been used as recognition elements for analytes in some of these biosensors.

Single-walled fullerene carbon nanotubes (SWNTs) have been used as probe tips for scanning probe microscopy imaging with molecular-level resolution.

APPLICATIONS:

- An important pharmaceutical application of nanotechnology is in the use of nanotubes for the extraction and chiral separation of drug analyte. Nanotubes can be used to selectively sequester lipophilic drugs and analytes to separate them from aqueous solutions.
- Enantio separation of drugs can be achieved using antibody-based bio-nanotubes as antibodies can have selectivity for single enantiomers.
- Nanotubes are also used in stochastic sensors to detect analytes, such as metal ions and small organic molecules. Microfluidic devices have automated and scaled-down

separation and chemical reactions of analytes.

- It has been possible to introduce attoliters (10−18 l) of drug samples into separation capillaries for analysis. Zeptomole (10−21 mol) detection limits for proteins can be achieved even through picoliter (10−12) sample volumes.
- Nanomachines and nano-objects are fast becoming a new tool in the arsenal of pharmaceutical analysts. In the near future, these nanodevices could become commonplace in pharmaceutical analysis and drug discovery processes.

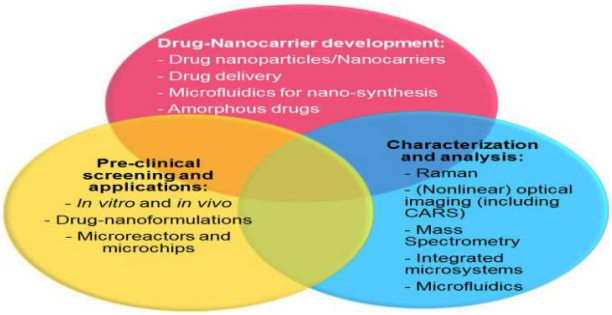

Figure.2:Applications in nanotechnology

IMPORTANCE:

Nanotechnology will have an increasingly important role in the development of commercial analytical and preparative tools. Nanodevices that are being realized or envisaged as biotechnological tools for the future include biosensors at nano-levels, nanosamplers, cell orienters, Nano analyzers, nanoarrays and nanofluidics. In the years to come, nanotechnology is likely to lead to many exciting biomedical and biotechnological applications, including pharmaceutical analysis.

5. MICRODOSING STUDIES:

Microdosing, or **micro-dosing**, is a technique for studying the behaviour of drugs in humans through the administration of doses so low ("sub-therapeutic") they are unlikely to produce whole-body effects, but high enough to allow the cellular response to be studied. This is called a "Phase 0 study" and is usually conducted before clinical Phase I to predict whether a drug is viable for the next phase of testing. Human Microdosing aims to reduce the resources spent on non-viable drugs and the amount of testing done on animals.

Less commonly, the term "Microdosing" is also sometimes used to refer to precise dispensing of small amounts of a drug substance (e.g., a powder API) for a drug product (e.g., a capsule),and when the drug substance also happens to be liquid this can potentially overlap what is termed “Microdispensing”.For example, “LSD-Microdosing”.

TECHNIQUES:

The basic approach is to label a candidate drug using the radioisotope carbon-14,and then administer the compound to human volunteers at levels typically about 100 times lower than the proposed therapeutic dosage (from around 1 to 100 micrograms but not above).How the body responds. For example, its conversion of the original drug into other molecules, and how long they stay in the body. The amount of radioactivity administered is typically around 200 Nanocuries. This is low as to be considered ‘non-radioactive’ by authorities.As only microdose levels of the drug are used, analytical methods are limited. Extreme sensitivity is needed.

Accelerator Mass Spectrometry is the most common method for microdose analysis. AMS was developed in the late 1970s from two distinct research threads with a common goal, an improvement in radiocarbon dating that would make efficient use of datable material and that would extend the routine and maximum reach of radiocarbon dating. AMS is routinely used in geochronology and archaeology, but biological applications began appearing in 1990 mainly due to the work of scientists at Lawrence Livermore National Laboratory. AMS does not measure the radioactivity of carbon-14 in microdose samples. AMS, like other mass spectrometry methods, measures ionic species according to mass-to-charge ratio.

Figure.3: Accelerator mass spectrometer

The technique has been developed commercially and in 2005, trials were conducted with several major pharmaceutical companies in the CREAM (Consortium for Resourcing and Evaluating AMS Microdosing) trials, in which Microdosing was used to predict the behaviour of five drugs, each with idiosyncrasies that had proved problematic in animal testing. The results pointed to a 70 percent correspondence between the results obtained using Microdosing and those obtained from full-dose studies. In 2006 an EU-funded Microdosing collaboration was formed to test the relationship between a microdose and therapeutic dose of another seven drugs.

IMPACT OF USE:

It is reported that 15 of the 20 largest pharmaceutical companies have now used Microdosing in drug development, and the use of the technique has been provisionally endorsed by both the European Medicines Agency and the Food and Drug Administration. It is expected that by 2010, human Microdosing will have gained a secure foothold at the discovery-preclinical interface driven by early measurement of candidate drug behavior in humans and by irrefutable economic arguments.

In January 2006, the European Union Micro dose AMS Partnership Program (EUMAPP) was launched. Ten organizations from five different countries (United Kingdom, Sweden, Netherlands, France and Poland) will study various approaches to the basic AMS technique.

One of the most meaningful potential outcomes of Phase-0/Microdosing studies is the early termination of development. In 2017, Okour et al published the first example in literature of a termination of an oral drug based on IV microdose data. This study provides an example of the application of micro dosing in circumstances where pre-clinical data were not sufficient to provide accurate information to guide first-in-human (FIH) study design.

6. CHEMOMETRICS:

Chemometrics is the use of mathematical and statistical methods to improve the understanding of chemical information and to correlate quality parameters or physical properties to analytical instrument data. Patterns in the data are modeled; these models can then be routinely applied to future data in order to predict the same quality parameters.

The result of the chemometrics approach is gaining efficiency in assessing product quality. It can lead to more efficient laboratory practices or automated quality control systems. The only requirements are an appropriate instrument and software to interpret the patterns in the data.The science of chemometrics gives spectroscopists many efficient ways to solve the calibration problem for analysis of spectral data.

Chemometrics can be used:

To enhance methods development and make routine use of statistical models for data analysis. Spectroscopists use software packages like The Unscrambler® for spectroscopic data analysis, modeling, classification and prediction to meet process monitoring and quality assurance needs. The spectroscopist's chemo metrics requirements are:

- Proper application of spectroscopic data pre-processing, to reduce and correct interferences such as overlapped bands, baseline drifts, scattering, and path length variation.
- Model validation and integration means to supply rigorous prediction, measurement QC and real-time product quality and process monitoring. Spectroscopists need to use the following methods within a

chemometrics software package to explore their data:

- Principal Component Analysis (PCA)
- Regression (PLS, PCR, MLR, 3-way PLS) and Prediction
- SIMCA and PLS-DA Classification
- Design of Experiments
- ANOVA and Response Surface Methodology
- Multivariate Curve Resolution (MCR)
- Clustering (K-Means)

Chemometrics is the bridge between connecting the state of a chemical system to the measurements of the system. It has become an essential part in the modern chemical and biomedical industries. Chemometrics software has been widely used by product development scientists, process engineers, PAT specialists, and QA/QC scientists to build reliable model, ensure product quality, classify raw material, and to monitor process end point in real-time.

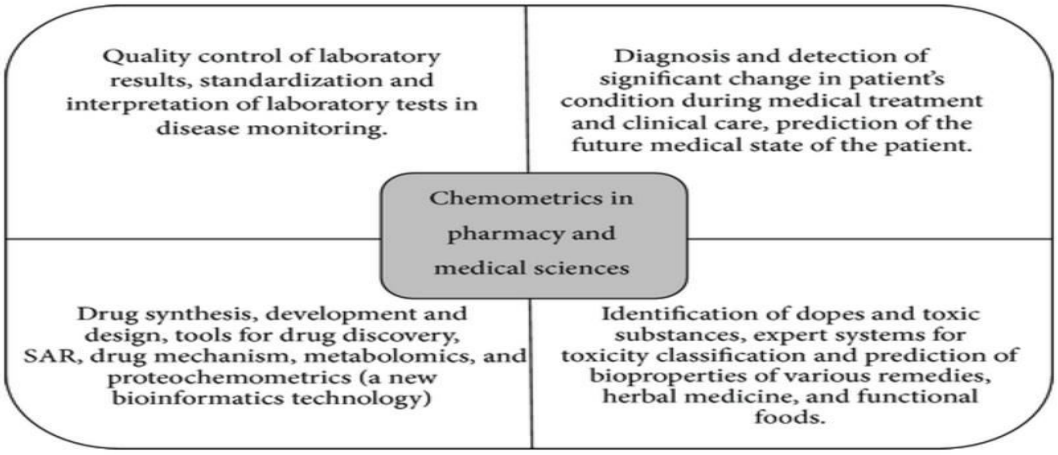

Figure.4: Applications in chemometrics

AT A GLANCE

- Chemometrics uses mathematical and statistical methods to improve understanding of chemical information.
- Chemometrics gives spectroscopists efficient ways to solve the calibration Problem for analysis of spectral data.
- Spectroscopists use software packages for data analysis, modeling, classification and prediction.
- Chemometrics has become an essential part in the modern chemical and biomedical industries

CONCLUSION:

As the pharmaceutical industry embraces new approaches, R&D costs might rise in the short term as a result of the unprecedented number of novel drug targets. The cost of analysis could also escalate at certain points in the development timeline. Only time and experience will tell whether the new technologies and advances have delivered their promise of potential benefits.

- As researchers combine available analytical tools, develop new technologies and find new applications for existing technologies, the search for new drugs and vaccines continues. The cooperation of industry players, regulators, researchers, healthcare professionals, patients and the public is necessary to achieve a win-win situation for all.

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