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Future Drug Discovery

Role of pharmaceutical sciences in future drug discovery

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The recent emergence of COVID-19 influenced the layman's knowledge of drugs. Although several drugs have been discovered serendipitously, research has moved to the next-generation era of drug discovery. The use of drugs is inevitable and they have become lifesavers in the present era. Although research from different scientific backgrounds has supported the translational research of drug discovery, the prime role of pharmacy has to be remembered. Here we have summarized the role of some important subjects in pharmacy education, which have paved different ways in drug discovery and development.

Lay abstract: Despite existing therapies for various ailments, emerging diseases or disorders need more selective treatments. Traditionally 'pharmacy' is thought of as a medical store, but time has changed pharmacy into a multidisciplinary subject with core research domains, including pharmacognosy, pharmaceutical biotechnology, pharmaceutical analysis, pharmaceutical chemistry, pharmacology and pharmaceutics. The main objective of these subjects is to provide strong support for both basic and translational research. Here we summarize the role of each of these domains of pharmaceutical science in the design and development of pharmaceuticals.

Tweetable abstract: How pharmacy's core research domains provide strong support for both basic and translational drug discovery research.

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Keywords: bioinformatics • drug discovery and development • pharmaceutical analysis • pharmaceutical biotechnology • pharmaceutical chemistry • pharmaceutical engineering • pharmaceutical research • pharmaceutics • pharmacognosy • pharmacology • pharmacy • statistics

The use of drugs in daily life has increased in recent years due to the emergence of new diseases and chronic disorders [1]. In addition, due to our present lifestyle (i.e., exposure to harmful pollutants and micro-organisms), novel and safer pharmacological treatments are heavily needed. Therefore the runaway progress of drug discovery and development is inevitable, and it is reasonable to expect the emergence in a short time of outcrops of large

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pharmaceutical companies. Pharma professionals have become pillars of various research and development centers, including public and private organizations and foundations.

The word 'pharmacy' is derived from the Greek word pharmakon (φάρμακον), which means remedy (in terms of pharmacology) or poison (in terms of toxicology) [2]. Although the profession of pharmacy has existed since the year 2600 BCE, it was popularized by three main people: Aelius Galenus or Claudius Galenus (130–200 AD; father of pharmacy), William Procter Jr. (1817–1874; father of American pharmacy) and Mahadeva Lal Schroff (1902–1971; father of Indian pharmacy education) [3].

Although the exact definition of 'pharmacy' is not established yet, it represents a scientific profession which instructs an "art or practice of preparing, preserving, and compounding medicines and dispensing them according to prescriptions" [4]. However, considering recent developments, the time has come to rework the definition. Despite other invaluable scientific fields [5–7], in recent days the pharmacy field has become a key component, particularly in the development of successful new diagnostics, prophylactics and therapeutics.

Despite its professional integrity, the subjects of pharmacy are multidisciplinary. The field deals with all the areas of drug development, from preclinical research to clinical research and patient compliance. Pharmaceutical researchers are involved throughout the drug discovery process, including the transition of a drug candidate from preclinical research to its clinical stage. In the early stages of drug discovery and development (the preclinical stage), pharmacy subjects such as pharmcognosy, pharmacoinformatics, pharmaceutical chemistry, pharmaceutical analysis, pharmacology and pharmaceutics are included in the drug discovery process. In later stages, doctors of pharmacy and professionals working in pharmacovigilance, regulatory affairs, pharmaceutical management and other subjects co-operate within the clinical stage of drug discovery (Figure 1).

Previously, it was biologists who discovered new targets [8] for prophylaxis and therapy and were regarded as the core scientists; however, this notion has been changed over time because each translational subject is applying prospective and retrospective methods to discover novel targets and their inhibitors or activators in disease settings. In parallel with the other scientific domains, such as medical and basic science and others, pharmacy is also now more closely involved in the drug discovery and development process. Pharmacy has become an established scientific field, as such diversified prophylactic and therapeutic interventions are developed (e.g., biologics, vaccines, biosimilars and chemicals). With the help of advanced DNA sequencing, bioinformatics tools, quick extraction processes, rational medicinal chemistry approaches, pharmaceutical compositions and others, it is doable to prepare libraries of small bioactive molecules and contribute to drug development. Irrespective of the source and strategy, these new chemical entities are sources for the downstream drug discovery and development process [9]. Interestingly, the conventional subjects of degrees are being redesigned and renamed under the umbrella of pharmacy. Moreover, apart from drugs and cosmeceuticals, pharmacy has made enormous contributions toward the development of pesticides for agriculture [10,11]. Schools of pharmacy are being established in the majority of universities and foundations all over the world.

In this commentary piece, we will address the global role of pharmacy in drug discovery and development and shed light on each subject's role in future drug discovery.

Pharmacognosy

Pharmacognosy is derived from two Greek words: pharmakon ('drug') and gnosis ('knowledge'); that is, it means 'drug knowledge'. CA Seydler, a German who coined the term 'pharmacognosy' in his book *Analecta Pharmacognostica* in 1815, was named the 'Father of Pharmacognosy' [12].

Pharmacognosy is the study of natural products obtained from numerous sources such as herbs, shrubs and trees. Along with the primary metabolites, in particular, it deals with secondary metabolites, including alkaloids, glycosides, tannins, steroids, terpenoids and phenolic compounds obtained from natural origins. Despite the existence of many synthetic drugs, natural compounds are often used in the prevention and treatment of a wide range of diseases worldwide.

Historically, secondary metabolites from natural products and their derivatives have produced the majority of new drugs. Many essential medicines – aspirin, morphine, atropine, digitoxin, quinine, pilocarpine, galanthamine and others (Figure 2) – have been obtained from natural sources and are still used as gold standards in drug discovery [13]. Observing the number of drugs discovered and developed into final drug entities demonstrates the importance of pharmacognosy in therapy. Among 1562 drugs approved between 1981 and 2014, 396 (26%) were purely natural products or derived from them [14,15]. The rate of new chemical entity (NCE) approvals also reveals that the natural products field produced, or was involved in, 25–30% of all small molecules in 2014 [15]. For example, in

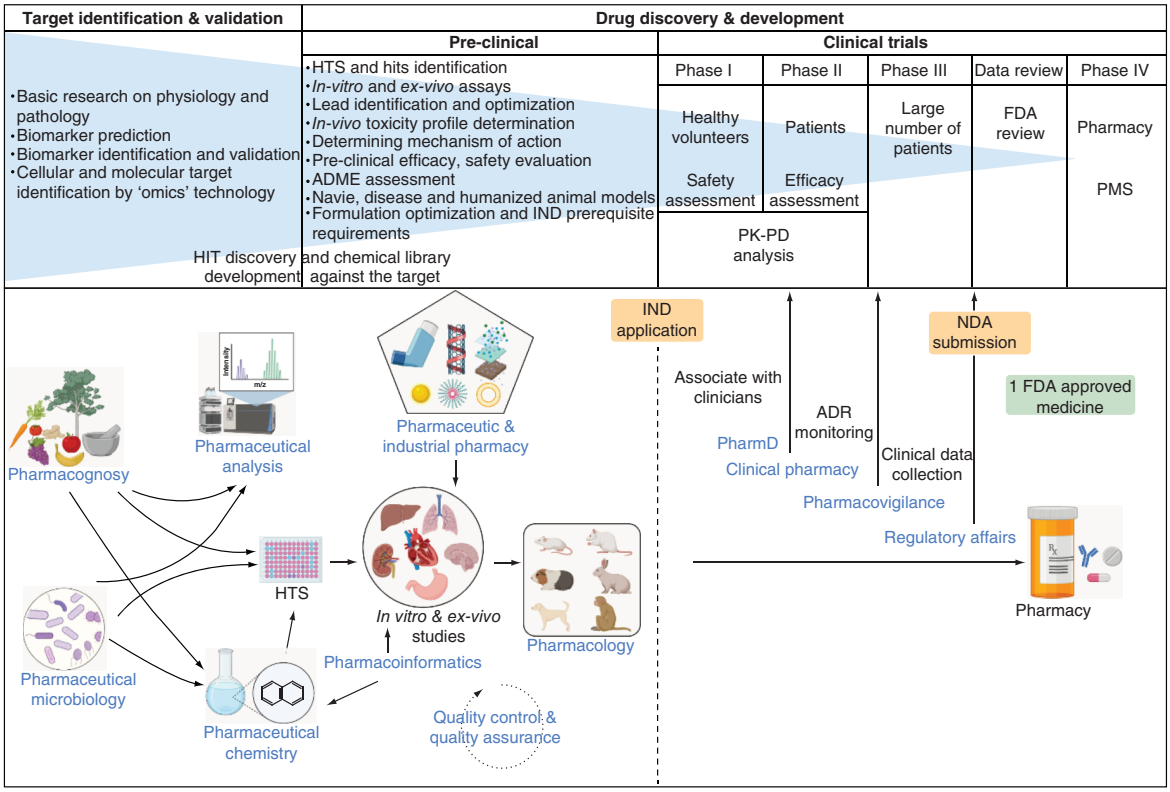

Figure 1. Global view of the role of pharmacy in drug discovery and development. The field of pharmacy has been diversified into many facets which are involved in each stage of drug discovery and development. In the above figure, each subject has been placed with respect to the function in drug discovery and development. Finding a target against a disease or disorder is the cornerstone to drug discovery and development. Several omics methods and screening procedures have been used in biomarker prediction. Upon validation of the biomarkers, chemical libraries are evaluated against the target by using high-throughput screening. Various *in vitro*, *ex vivo* and *in vivo* methods are helpful in the hit to lead optimization and mechanism of action determination. Once the lead drug candidate is selected, delivery systems and formulations composed of the lead drug candidate are optimized. Next, the lead drug candidate enters into clinical trials and is required to pass different phases (I–IV). After safety (Phase I) and efficacy (Phase II) assessment, the drug candidate is tested in a large number of patients (Phase III). The US FDA reviews the results and approves the medicine (if found suitable). In Phase IV, the drug is made available in the market and its performance is monitored via post-marketing surveillance.
ADME: Absorption, distribution, metabolism and excretion; ADR: Adverse drug reaction; HTS: High-throughput screening; IND: Investigational new drug; PD: Pharmacokinetics and pharmacodynamics; PK-NDA: New drug application; PMS: Post-marketing surveillance.

the area of anticancer drugs (vincristine, vinblastine, trabectedin, streptozocin, paclitaxel, pentostatin, peplomycin, asparaginase, doxorubicin, leucovorin, mithramycin, mitomycin C etc.), 93 of 246 (33%) natural products-based high molecular weight drugs and 56 of 136 (41%) natural products-based low-molecular weight molecules approved worldwide from 1940–2014 [15]. Natural products have a strong influence in other areas as well, especially anti-infective drugs (e.g., artemisinin, ivermectin, daptomycin, fidaxomicin, carumonam, fosfomycin trometamol, isepamicin, micronomicin sulfate, miokamycin, mupirocin, netilmicin sulfate, RV-11, teicoplanin); 96 of 326 such drugs were obtained from natural products and their derivatives, indicating the importance of pharmacognosy in drug discovery and development of anti-infective drugs [15]. A multidisciplinary approach to drug discovery, including the creation of genuinely new molecular diversity from natural products, will continue to be the greatest answer to the present productivity problem facing the scientific community involved in drug discovery and development [16]. Despite the fact that natural products have historically contributed a pivotal role in drug discovery and development, most pharma companies have drastically reduced their natural product operations in recent years. The cause for this is that natural products have extremely complex structures which are incredibly expensive to produce on a large scale. Penicillin, morphine and paclitaxel (Figure 2) are examples of such medications which can

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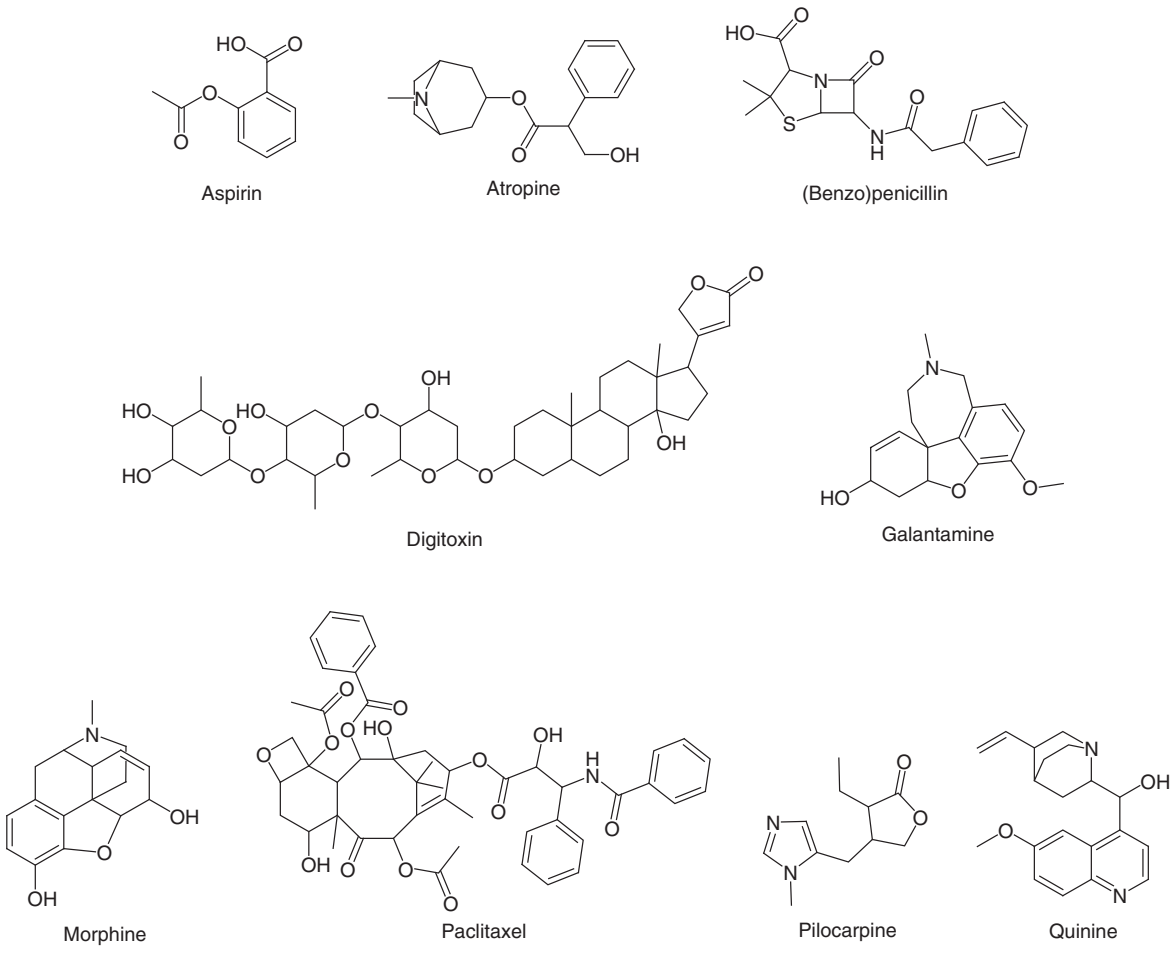

Figure 2. Structures of essential medicines.

only be obtained from their natural source, which can be time-consuming, expensive and potentially unsustainable for the resource. However, despite competition from other drug discovery approaches, natural products continue to provide a reasonable proportion of novel clinical candidates and drugs.

A multidisciplinary approach involving new natural product sources combined with full and combinatorial synthetic methods would be the best solution to the current efficiency challenge faced by the scientific community engaged in drug discovery and development [17]. Given that naturally occurring drugs cannot be mass produced, synthetic biosimilars must be developed. Increased bioavailability, altered pharmacokinetics and improved efficacy are all possible when these compounds are synthesized.

The biggest hindrance to bringing natural products to market is not isolation, simple semi-synthesis or complete synthesis, but the enormous supply issues that process chemists face when turning research laboratory developments into marketable products. Pharmacognosists have a wealth of knowledge that can be extremely useful in the development of drug discovery [18]. However, natural products and/or their novel chemical structures are still being used mainly to discover and develop the final drug entity.

Pharmacognosy is now prepared to meet the current and future demands of drug discovery and development. Novel, innovative approaches to improve and accelerate the integrated drug discovery and development process are expected to emerge as a result of advances in drug target elucidation and lead structure discovery. New technologies, such as automated separation methods, high-throughput screening (HTS) and combinatorial chemistry, are revolutionizing drug development (Figure 3). These technologies compensate for the inherent limitations of natural products and provide an exceptional opportunity for them to reclaim their place as a major source of drug discovery [19].

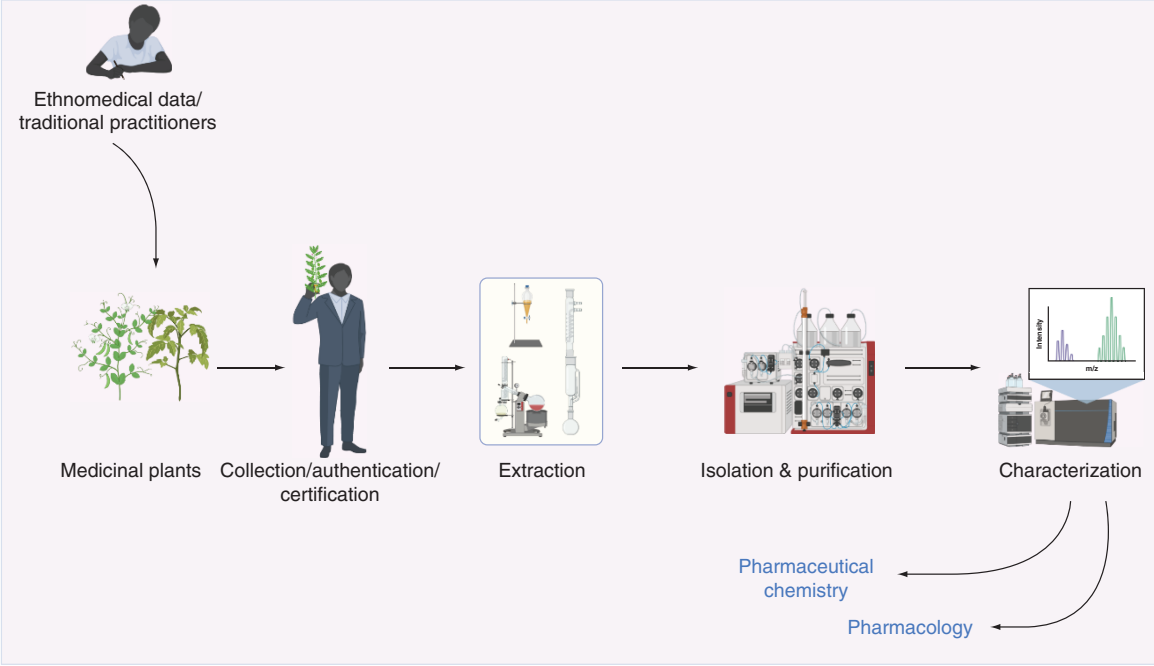

Figure 3. Role of pharmacognosy in drug discovery and development. The method begins with selecting medicinal plants from reliable sources, such as herbal monographs, ethnomedical data and traditional practitioners' knowledge. The process continues with plant collection, identification and authentication by a licensed botanist. The extraction and fractionation procedure then begins, utilizing methods like maceration, hot percolation, Soxhlet extraction, superficial extraction and microwave-assisted extraction. After that, pure compounds are isolated using chromatography methods, such as thin layer chromatography (TLC), high-performance TLC, gas chromatography–mass spectrometry, high-performance liquid chromatography and column chromatography, then utilizing structural characterization spectroscopy methods such as UV, IR, nuclear magnetic resonance and mass spectrometry. Sequentially, the method continues to pharmaceutical chemistry to discover a synthetic strategy for synthesizing the isolated compounds and then virtual screening to look for possible structural modifications (molecular modeling, quantitative structure–activity relationship, pharmacophores etc.). Finally, target-based bioassays/preclinical evaluations, including pharmacological evaluations in experimental animals (toxicology, pharmacokinetic and pharmacodynamic parameters), are performed on the isolated/structurally modified compounds.

Thus pharmacognosy is important in pharmacy and can continue to play an important role in education and the understanding of drugs and treatments. It should be one of the core topics in the course syllabus of all institutions offering pharmacy programs worldwide [20]. Natural product drug discovery has regained the pharma industry's focus and is on the edge of a revival, with access to modern technical contributions that offer higher returns on investment.

Pharmaceutical biotechnology

Pharmaceutical biotechnology is at the core of most methodologies now in use for drug discovery and development of both biologics and small molecules. Recombinant DNA and hybridoma technologies are widely employed in the manufacture of biopharmaceuticals. These techniques have revolutionized the biopharmaceutical market, and their growth has been enormously increased over the last decade [21,22]. Although production is costly compared with that of small molecules/synthetic drugs, their selectivity and specificity make them useful in critical conditions. Devolving to an individual cell to harvest the information found at the human genome level, revolutionary technologies and biotechnology techniques have contributed to advancements in drug discovery and research. These are 'omics' techniques: genomics (structural and functional), transcriptomics, proteomics, microarrays, pharmacogenomics, metabolomics, epigenomics, toxicogenomics and microbiomics have changed the new drug discovery paradigm and produce voluminous data to store and analyze. This generation of data has led to the big data era. In this era, data mining, a subfield of bioinformatics, is used in identifying and extracting relevant information.

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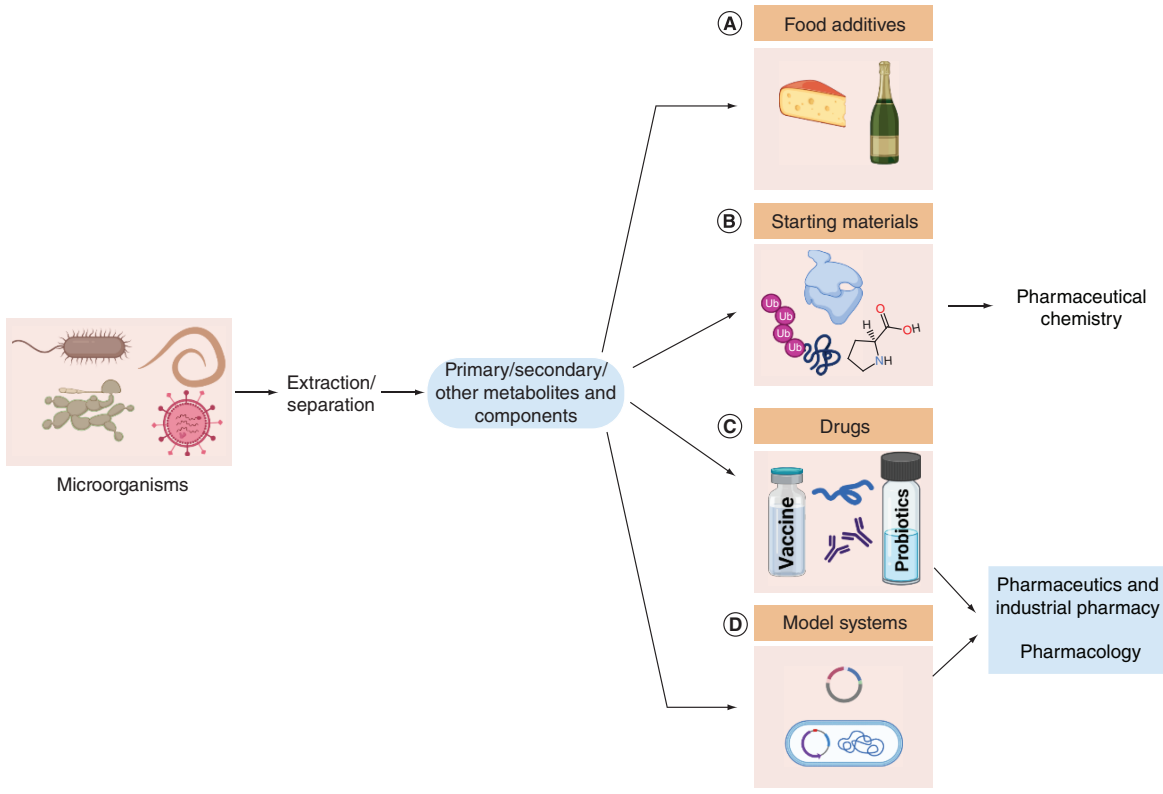

Figure 4. Role of pharmaceutical biotechnology in drug discovery and development. The process begins with isolation and identification of a particular microbial strain and its growth on a large scale in a bioreactor by providing nutritional requirements and optimal bioprocess parameters under controlled conditions for the production of metabolites/whole cells/cell components/modified cells. After extraction/separation and purification of the culture broth, purified metabolic products/cell components/cells/genetically modified cells may be obtained. **(A)** The whole pure culture may be used as a food additive in the baking or brewing industry. **(B)** A primary or secondary metabolite may be used as a starting material for the synthesis of drugs or as a drug itself. **(C)** Cell components or whole viable cells may be used in the manufacturing of vaccines or probiotics or for the production of monoclonal antibodies. **(D)** Genetically modified cells may be used for the expression of therapeutically useful proteins.

It is essential to accelerate the biotechnology-related research; the promise of omics techniques, bioinformatics and big data has opened new horizons for drug discovery at the root level.

Now researchers are involved in the task of converting DNA sequence data into information that will improve or even change drug discovery and personalized medicine. Pharmaceutical scientists are prepared to take advantage of omics technologies in new drug discovery and development. The etiologies of some complex diseases, like obesity and heart disease, can be well understood at a molecular level by adopting omics technologies. The success of sequencing the human genome is one of the greatest scientific achievements in the domain of medicine and biology. The sequencing of the human genome and the advent of other technologies to edit it have brought a major shift in medical research and clinical practice, which now aims toward an understanding of disease and its etiology, and truly personalized medicine at the molecular level.

The three key elements which must necessarily interact for modern drug discovery are: identification and validation of new drug targets; rapid and sensitive bioassays utilizing HTS methods; and the discovery of new molecules and their optimization employing these biotechnological techniques (Figure 4). At each stage, the key elements are now justifiable by bioinformatics and big data.

Pharmaceutical chemistry

The first modern chemist was Robert Boyle, who published the book *Sceptical Chymist* in 1661. Just over 100 years later, the French chemist Antoine Lavoisier determined that oxygen was a key substance in combustion

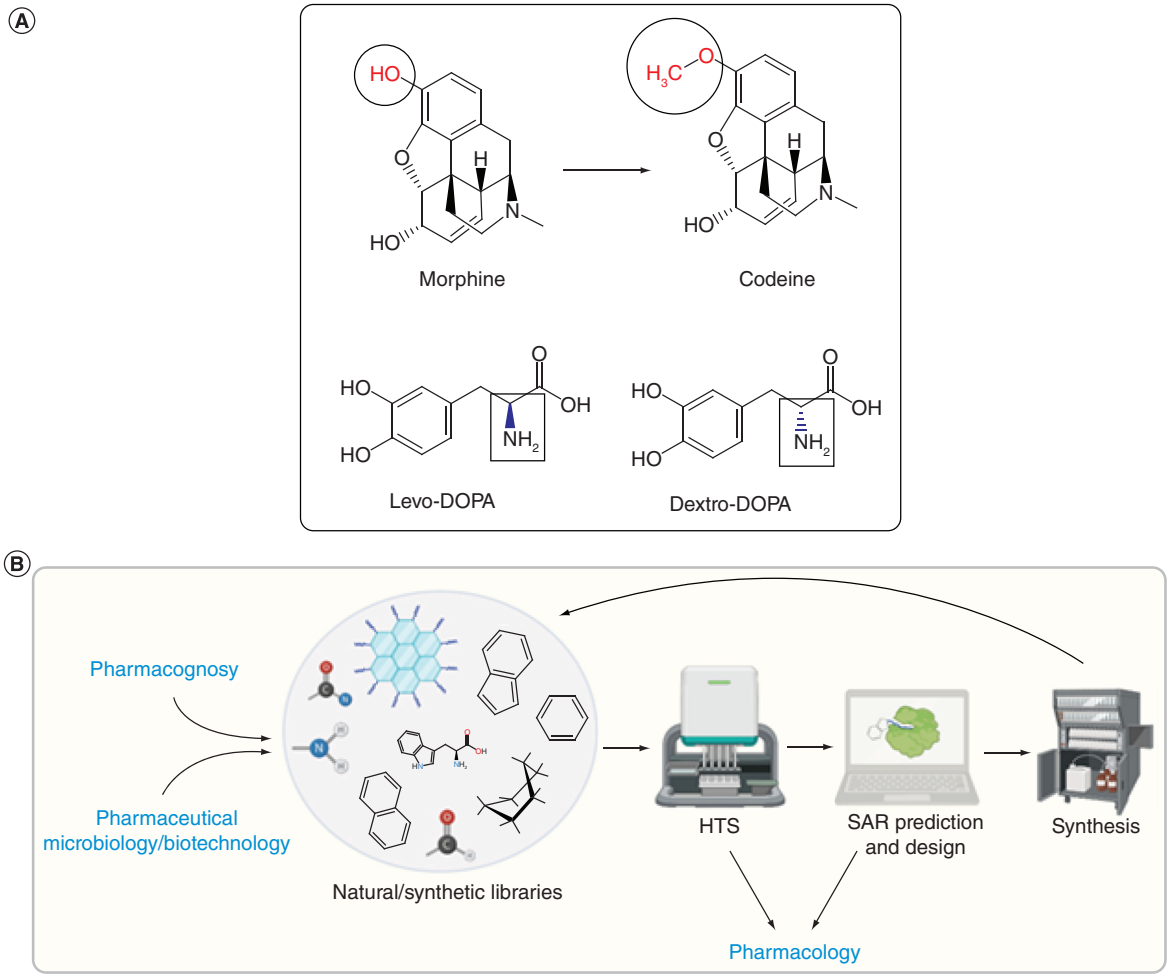

Figure 5. Role of pharmaceutical chemistry in drug discovery and development. (A) SAR of morphine, codeine, L-dopa and D-dopa. **(B)** Natural/synthetic libraries are evaluated against biological targets like receptors, inhibitory or excitatory neurotransmitters by using HTS. Active compounds which exhibit high potency and low side effects are determined through SAR studies based on the structure of lead compounds developed through HTS. Further, the synthesized chemical libraries are screened through SAR for their specific activity against various disease animal models (preclinical studies).
HTS: High-throughput screening; SAR: Structure–activity relationship.

and developed the modern system of nomenclature for chemicals and is hence regarded as the father of modern chemistry.

By early 1975, the drug discovery process mainly entailed synthesizing large samples of new chemical entities and screening them for a broad range of pharmacological activity in different animal models representing a disease state. Medicinal chemists usually synthesize new chemical compounds with structural similarity to natural products or known drugs. However, a major revolution started in the 1980s when chemists began synthesizing compounds to focus on discrete molecular targets like receptors, enzymes and ion channels. In the 1990s, structure-based drug discovery was an emerging field to identify the lead compound. In the 2020s, numerous technological advances have been introduced into the drug discovery process, such as high-throughput synthesis (HTS), genomics, computational chemistry and structural biology [23].

Medicinal chemistry plays a pivotal role in the process of drug discovery, as the biological activity of any drug molecule depends entirely on its 3D structure; hence it is essential to understand the chemistry through structure–activity relationship studies at the initial stages of the drug discovery process [24]. For example, the well-known compound morphine exhibits maximum analgesic potency at a lower dose due to a free hydroxyl group at the C-3 position (Figure 5A) of its structure which interacts with opioid receptors; however, the blocking of the C-3 hydroxy

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group in codeine causes a reduction (Figure 5A) to one-tenth of the analgesic activity compared with morphine at the same dose [25]. Thus study of the structure–activity relationship plays a crucial role in identifying a better hit molecule with high specificity, selectivity and limited side effects by considering its pharmacodynamic properties, like the nature of its its pharmacophore or heterocyclic ring system, as well as pharmacokinetic properties such as absorption, distribution, metabolism and excretion, which mainly depend upon the presence of substituents on a heterocyclic ring system (Figure 5B). The partition coefficient is a key parameter for absorption and distribution of any drug molecule in the body and also affects permeability through the blood–brain barrier, which mainly depends on the presence of polar and nonpolar groups in the structure of a drug molecule; for instance, polar groups such as -OH, -SH and -NH_2 enhance hydrophilicity, thereby limiting CNS side effects effectively. On the other hand, the presence of aliphatic moieties, such as carbon chains or cyclic ring systems, enhances hydrophobicity, which increases CNS activity [26]. Hence the presence of polar and nonpolar substituents on the pharmacophore influences the pharmacokinetic properties of a drug molecule. Major adverse effects are mainly due to inappropriate peripheral and central metabolic pathways caused by the presence of various substituents; hence it is essential to replace those substituents with a bioisosterically similar replacement group to improve the selectivity. The best example to illustrate why medicinal chemistry plays a vital role in the drug discovery process is the case of thalidomide treatment, which resulted in severe birth defects (phocomelia) in thousands of children because of a small stereochemical change in the structure [27]. Therefore it can be seen that a small change in the structure of any drug molecule causes major health concerns. Another example of structural specificity is L-dopa (Figure 5A), which is an active compound for Parkinson's disease, whereas D-dopa (Figure 5A) is inactive. In recent days many advanced techniques have been introduced in the drug discovery process to develop highly selective drug molecules with limited toxicity; for example, molecular modeling and molecular imaging techniques. Molecular modeling provides a piece of knowledge on how the designed ligand can interact with receptors in the body, which can be proved in practice by molecular imaging techniques using a selective radioligand [28]. Hence with the predictions through bioinformatic studies, we can design a specific ligand that could reduce research cost, time and resources. The radioligands help in determining the receptor density, receptor occupancy, pharmacokinetic parameters and therapeutic doses of a new drug in preclinical and clinical studies of the drug discovery process.

Pharmaceutical analysis

Analytical chemistry began in the late 18th century with the work of Lavoisier and others, which was further developed in the nineteenth century by Carl Fresenius and Karl Friedrich Mohr. As a pharmacist's apprentice in Frankfurt, Germany, Fresenius developed an extensive qualitative analysis scheme, where he trained students in gravimetric techniques that he had developed [29,30]. Mohr developed laboratory devices, such as the pinch clamp burette and the volumetric pipette, and also devised a colorimetric end point for silver titrations. It was his 1855 book on titrimetry, *Lehrbuch der Chemisch-Analytischen Titromethode*, that generated widespread interest in the technique [29,30].

Later on, with the contributions and inventions of many scientists, the field of pharmaceutical analysis – which deals with the identification, characterization and quantification of substances in raw materials, dosage forms and biological samples – evolved. The substances of interest to be identified, characterized and/or quantified in a given pharmaceutical sample could be pharmacons (investigational drugs), active pharmaceutical ingredients, drug metabolites, impurities or degradation products. The analysis of drug substances involves several analytical techniques, including simple classical methods of analysis such as titrimetry and instrumental methods of analysis (spectroscopic and chromatographic methods). Nowadays, pharmaceutical analysis has been advanced by the utilization of modern hyphenated instrumentations, such as liquid chromatography–mass spectrometry (LC–MS), liquid chromatography with tandem mass spectrometry (LC–MS/MS) and liquid chromatography with parallel nuclear magnetic resonance and mass spectrometry (LC–NMR–MS), which are utilized in drug discovery and development (Figure 6).

The involvement of the three pillars of pharmaceutical analysis – identification, characterization (determination of physicochemical properties) and quantification of substances – starting from the early stages of candidate drug discovery is a clear indication that pharmaceutical analysis plays a pivotal role in drug discovery and development. Wherever the source (be it natural or synthetic) for an investigational drug candidate, first of all, its identity and purity should be determined by suitable analytical methods. For instance, in the discovery and development of a potential drug candidate from natural sources, chromatographic techniques such as thin layer chromatography (TLC) and paper chromatography play a crucial role in isolation and purification of investigational drug candidates.

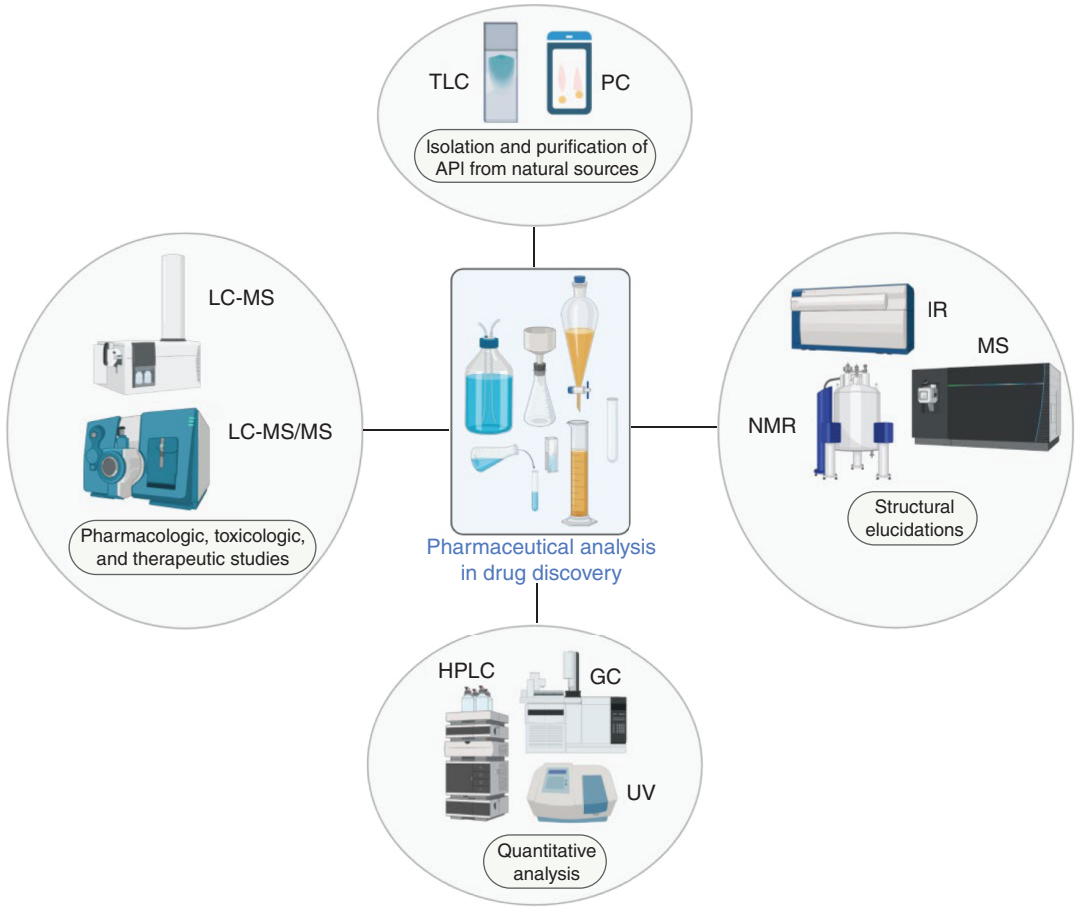

Figure 6. Role of pharmaceutical analysis in drug discovery and development. Chromatographic analytical methods, such as thin layer chromatography and paper chromatography are utilized for the isolation and purification of active pharmaceutical ingredients from natural sources. The structural elucidation of an investigational drug from a natural or synthetic source is achieved by instrumental analytical methods such as IR spectrophotometry, MS and NMR. The quantitative investigation of drugs within the process of drug discovery and development is performed by different instrumental methods of analysis such as high-performance liquid chromatography, gas chromatography and UV spectrophotometry. During the clinical stage of drug development, bioanalytical investigations that support pharmacological, toxicological and therapeutic studies will be performed by highly sensitive hyphenated instrumental methods of analysis, such as LC–MS and LC–MS/MS.
API: Active pharmaceutical ingredients; GC: Gas chromatography; HPLC: High-performance liquid chromatography; LC–MS: Liquid chromatography–mass spectrometry; LC–NMR–MS: Liquid chromatography with parallel nuclear magnetic resonance and mass spectrometry; NMR: Nuclear magnetic resonance; MS: Mass spectrometry; PC: Paper chromatography; TLC: Thin layer chromatography.

The structural elucidation of these potential drug candidates from natural sources is performed by compiling analytical data from the three important spectroscopic techniques, namely IR spectrophotometry, nuclear magnetic resonance (NMR) and mass spectrometry (MS). Analytical determinations by these three methods have also been employed in confirming the structure of synthetic drug candidates. High-performance liquid chromatography and gas chromatography, coupled with different detection systems, have been employed in quantification activities in discovering candidate drugs from natural and synthetic sources.

Pharmaceutical analysis is also an integral part of subsequent drug development following candidate drug characterization. Bioanalytical methods now undertake the lion's share of these subsequent studies performed on candidate drugs in the drug development stage with the aim of establishing pharmacological, toxicological and therapeutic data. In this regard, the modern hyphenated analytical techniques, such as LC–MS, LC–MS/MS and LC–NMR–MS, which are fast, selective and sensitive, are often utilized in the bioanalysis. These techniques are used in pharmacokinetic, pharmacodynamic and toxicological studies.

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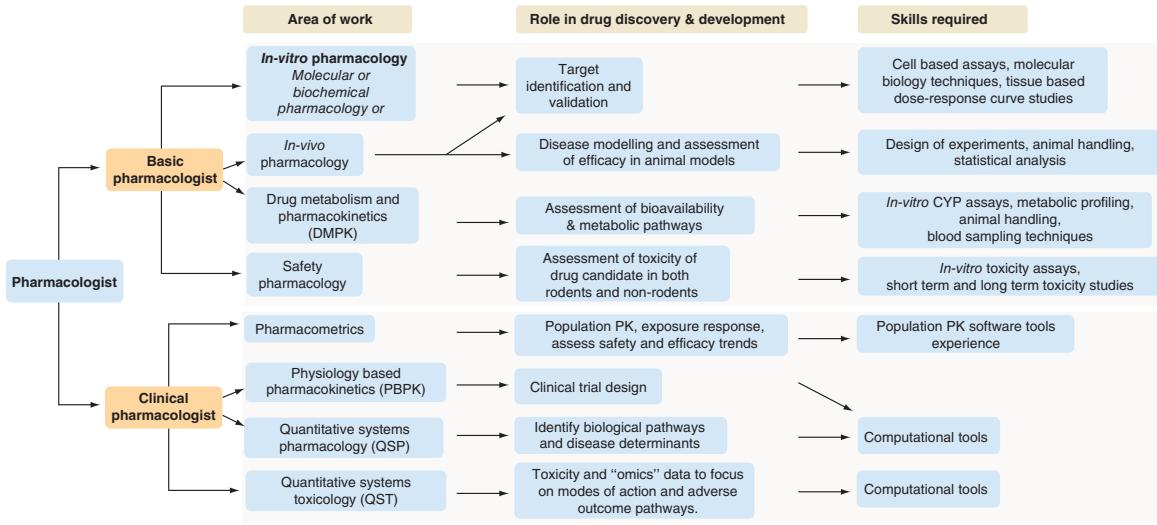

Figure 7. Schematic representation of the role of pharmacologists in drug discovery and development. Pharmacologists play an essential role in: molecular or *in vitro* pharmacology, which is considered important to identify and validate therapeutic targets, including receptor binding studies which are useful to calculate the IC_{50} values of the new NCEs; *in-vivo* pharmacology studies – efficacy studies that determine the median effective dose of the NCE, or *in vivo* studies conducted in knockout or transgenic animals to identify and validate the therapeutic target; drug metabolism and pharmacokinetic studies to determine the bioavailability and metabolism of NCEs, with the NCEs that possess sufficient bioavailability entering subsequent efficacy and safety studies; and safety pharmacology, which again includes both *in vitro* and *in vivo* studies, to determine the safety of the NCEs. Clinical pharmacologists actively participate in: physiology-based pharmacokinetics, which helps in clinical trial design, first-in-human dosing etc.; pharmacometric modeling and population pharmacokinetic studies, which help to fix dosing in special populations; quantitative systems pharmacology and quantitative systems toxicology, both of which are computational models used to predict biological pathways, drug pharmacology and drug toxicology, respectively. CYP: Cytochrome P450; NCEs: New chemical entities; PK: Pharmacokinetics.

The advancement of technologies and their implementation with artificial intelligence in machine learning technologies for pharmaceutical instrumentation truly exemplifies the drug discovery stages with a high speed and great accuracy. Furthermore, the design of experiments and the availability of methods such as analytical quality by design show a pivotal role in the current analytical techniques in the pharmaceutical approach. Thus, pharmaceutical analysis is one of the important pillars of drug discovery and can continue to play a crucial role.

Pharmacology

Pharmacology is the science of drugs (in Greek: pharmakos, medicine or drug; and logos, study). François Magendie was a French physiologist, considered a pioneer of experimental physiology. In 1809, he studied the effect of nux vomica (a plant-derived drug containing strychnine) on dogs and demonstrated that the spinal cord was the site of its convulsant action [31]. Jonathan Pereira (1804–1853; father of pharmacology) was an author of the *Elements of Materia Medica*, a standard work [32]. Rudolf Buchheim (1820–1879, originator of experimental pharmacology) introduced the bioassay to pharmacology and created a methodology for determining the quantitative and medical aspects of chemical substances [33]. Oswald Schmiedeberg (1838–1921; the founder of modern pharmacology) was a professor of pharmacology at the University of Strasbourg. He studied chloroform (anesthetic), chloral hydrate (sedative and hypnotic) and muscatine (which stimulates the parasympathetic nervous system) [34].

Pharmacology is primarily defined as the study of substances that interact with living systems so as to prevent, ameliorate or cure the deleterious consequences of disease. Pharmacology is the cornerstone of drug discovery and development. As well as their important role in basic research, pharmacologists have become an integral part of the team in both preclinical and clinical research (Figure 7). *In vitro* pharmacology studies deal with biochemical, cellular and biophysical assays over a wide range of biological target classes (e.g., G-protein-coupled receptors, kinases, ion channels and protein–protein interactions) in order to identify and validate the therapeutic target during the drug discovery process. Furthermore, *in vitro* studies, such as receptor binding studies, help to determine the potency and specificity of new chemical entities (NCEs) [35]. *In vivo* pharmacology is the

study of the biological effects of a drug in a complex living organism and is used to observe the complex physiological effects of a drug. Used in animal models that mimic human disease, these studies are also known as efficacy studies. Before the drug candidate is tested for efficacy, it is imperative to conduct a pharmacokinetic evaluation to ensure that it is bioavailable in the animal models. Because pharmacologists better understand pharmacokinetic principles, they are considered more suitable for conducting drug metabolism and pharmacokinetic studies [36]. Once an NCE passes the bioavailability test in animal models, it moves to the next level to assess efficacy. The most important part of preclinical research is inducing the disease in various animal models that mimic the human disease [37]. Pharmacological safety studies are carried out to assess any potential undesirable effects of the drug on the body's major systems. Although the majority of safety testing of pharmaceuticals was carried out on animals, today safety tests are increasingly performed using *in vitro* models that involve isolated cell lines and tissues [38]. On the other hand, physiology-based pharmacokinetics helps to make research and development decisions relating to clinical trial design, first-in-human dosing, formulation design, dosing in special populations and predictions of drug–drug interactions [39]. Pharmacometric modeling includes population pharmacokinetics, exposure–response and disease state modeling to predict clinical outcomes and assess safety and efficacy trends across exposure ranges [40]. Similarly, clinical pharmacology in drug development includes quantitative systems pharmacology and quantitative systems toxicology modeling. The former is a discipline within biomedical research that uses mathematical computer models to identify biological pathways and disease determinants and drug pharmacology [41], while the latter combines toxicity and omics data to focus on modes of action and adverse outcome pathways [42]. Recently a particular branch of pharmacology, immunopharmacology, has become most popular; it deals with drugs, vaccines, monovalent and polyvalent antibodies, and other substances which are involved in immunology and pharmacology intervention [43].

Pharmaceutics & pharmaceutical engineering

Pharmaceutics deals with the presentation of the drug in a patient-friendly dosage form. The feasible dosage form, route of administration and time of administration are determined within this specialization. The pharmaceutical dosage forms include tablet, capsule, solution, suspension, emulsion, semisolids, sterile dosage forms, controlled drug delivery systems and specialized formulations such as nanoformulations and particulate drug delivery systems. Physical pharmacy, pharmaceutical engineering, pharmaceutical product development and biopharmaceutics and pharmacokinetics are different branches of pharmaceutics involved in drug design and discovery and the development of drug products (Figure 8) [44,45]. Scientific knowledge in these areas is required to optimize the properties of the drug and to enable the drug molecule to reach its target site.

Optimization of a lead compound involves identifying its crystallinity and the amorphous, polar, nonpolar or amphiphilic properties of the active pharmaceutical ingredient. The type of solid state exhibited by drug needs to be determined as it may exist in amorphous, polymorphic, pseudopolymorphic, salt or crystal form. The solubility, ionizability, stability and permeability are also required to be characterized and optimized during drug design.

Physical pharmacy deals with the fundamental concepts of the physical properties of drug molecules and their determination. Particle engineering has become important in drug discovery seeking to alter particle characteristics and to deliver better products. Solid-state manipulation is one of the key areas involved to alter a drug's physical, chemical, quality and performance attributes. To understand particle engineering, one must understand how particles form and the specific processes and techniques to formulate materials, such as milling, blending or granulation. Drug delivery can be affected by particle size, as it influences absorption, stability and targetability. For example, drug design for oral or nasal sprays, in particular, needs to consider particle size, which influences targetability to lungs; additionally, inhaled medicines with larger particles may damage the lungs. The principles and working operation of various unit operations are known from the subject of pharmaceutical engineering. The designed NCE must be presented as a suitably effective, acceptable, stable and safe pharmaceutical dosage form. The selection of suitable dosage form, composition and the process related to the development of dosage form need the concepts of pharmaceutical product development. The technical skills and knowledge related to product development are required to select excipients, characterize and optimize the finished pharmaceutical product and validate the process. The absorption, distribution, metabolism and excretion patterns regarding the administered drug are dealt with in the subject of biopharmaceutics and pharmacokinetics. The impact of physicochemical factors, pharmaceutical factors and biological properties on the bioavailability of drugs is studied in biopharmaceutics (Figure 8). The estimation of pharmacokinetic parameters, route of administration, dose and frequency of administration is based on the *in vivo* pharmacokinetics. The appropriate empirical, mathematical or computational model

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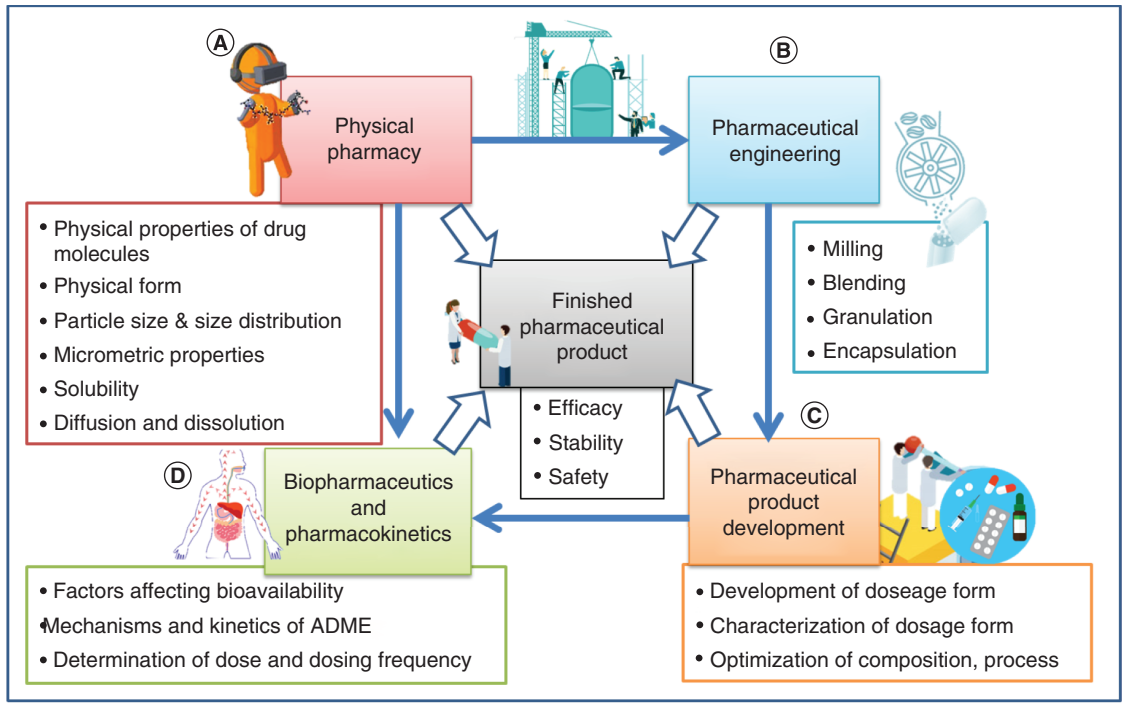

Figure 8. Pharmaceutical concepts in dosage form development. The key attributes of a new chemical entity are potency, selectivity and efficacy, which in turn are dependent on its absorption, permeability, stability. Dissolution is dependent on aqueous solubility, and permeability is dependent on lipophilicity, molecular size and charge. These properties are reflected in the rule of five. **(A)** Deals with the description of the physical pharmacy properties. **(B)** Manipulation and optimization of these properties (pharmaceutical engineering). **(C)** Deals with the formulation of a dosage form containing the molecule exhibiting drug-like properties. **(D)** The *in vivo* disposition of a compound is characterized by the pharmacokinetic parameters' clearance, the volume of distribution, their half-life and bioavailability.
ADME: Absorption, distribution, metabolism and excretion.

development needs the knowledge of pharmacokinetics, and emerging concepts like time-dependent pharmacokinetics (chronopharmacokinetics) and therapeutic drug monitoring are also founded on the fundamental concepts of pharmacokinetics. Further, the computer-simulated physiological models, application of 3D printing, machine learning and artificial intelligence in production, automation and evaluation of pharmaceutical dosage forms also need the basics of pharmaceutics [44,45].

Apart from drug discovery research for new molecules, excipient development is equally important for dosage form design of new biopharmaceuticals. In this regard, formulation scientists are researching various aspects of excipient development, safety/toxicology testing, regulatory processes, quality, manufacturability and the utility of different drug delivery systems. Now excipients constitute the major portion of the dosage form and they impact the reproducibility of manufacture and overall quality of the dosage form. This has forced academia and industry to develop a thorough understanding of functionalities and the possibility of utilizing suitable excipients in dosage form design. Particulate drug carriers are intended for the controlled and targeted delivery of active substances and the enhancement of their therapeutic performance by either physical or active targeting based on their physical properties and the ligand or the carrier used. The carriers' biodistribution and uptake into certain tissues or cells can be manipulated with a suitable formulation approach. They are used in oral, parenteral and other localized delivery applications (e.g., dermal, respiratory, ocular or nasal) [44,45].

The development, production and testing of pharmaceutical dosage involve a series of unit operations which may include milling, mixing, drying, filtration, evaporation or distillation, all of which are governed by certain engineering principles and application of material balance and energy balance. The design, operation and maintenance of various types of equipment in the pharmaceutical industry are based on pharmaceutical engineering principles. The unit operations and accompanying laws and mechanisms influence the quality, performance and

stability of the formulation and optimization of the process. Pharmaceutical engineering is applied throughout the life cycle of the pharmaceutical product, from the construction of the plant material to the finished dosage form.

Conclusion

The process of discovering new drugs includes several complex stages, yet it is fascinating. However, each stage involves a different area of study. Although the pharmacist's role is well known, the lack of clarity on each pharmaceutical science domain in drug development confuses aspiring pharmacists. Over the past decade, it is evident that pharmaceutical sciences have climbed to prominence in drug development research. There should be involvement by all pharmaceutical scientists in the drug discovery process (directly or indirectly), regardless of the domain, whether in academia or industry, conducting fundamental research or translational research from preclinical studies to hospital pharmacy.

Future perspective

Until recently, most literature was focused only on certain disciplines, such as chemistry or biology. There is a gap of knowledge presentation on pharmaceutical sciences and their key roles in drug discovery. Therefore this article presents a global view of pharmaceutical sciences and their involvement in drug discovery and development. Given the events of the recent COVID-19 pandemic, it is worth recollecting the importance of pharmaceutical industries in the development of vaccines and repurposed drugs, as well as emphasizing the role of pharmaceutical researchers in therapeutics development. For this reason, we aimed to illuminate the role of each major branch of pharmaceutical sciences here. Although the word 'pharmacy' is well known, the disciplines and research activities related to it are neither well known nor well captured in the literature. Therefore this review aimed to provide a broad overview of the pharmaceutical research in each domain.

Conventional methods of drug discovery and development are time-consuming; however, the new advanced technologies in the pharmaceutical sciences have sped up the process. Moreover, other fields not discussed in detail here, such as computer sciences and statistics, are involved throughout all disciplines. Based on the current progress, we presume that future drug discovery in the pharmaceutical industry will be advanced by the use of bioinformatics and other computer-assisted systems [46,47]. Despite a wide variety of computer applications, the potential for use of computer science or computational systems in drug discovery and development is immense. As a result, some leading areas in computer science – such as artificial intelligence, statistics, computer systems and networks, security, database management systems, software engineering, human–computer interaction, vision and graphics, programming languages, bioinformatics and computing theory – are contributing to well-known computer-assisted systems for drug discovery and development.

We are sure the coming generation will use computer science and technologies, particularly artificial intelligence (machines which function intelligently and independently; machine learning, deep learning, neural networks and others) in the field of pharmaceutical sciences, such as drug design, discovery, pharmaceutical product management and development, pharmaceutical product manufacturing, clinical trial design and monitoring.

Finally, the drug discovery and development process will be benefited by all disciplines of pharmaceutical sciences.

Author contributions

Irrespective of the order of the authors, all authors contributed equally.

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Executive summary

Background

- Despite developments in other scientific domains, pharmaceutical research has come to the forefront of drug discovery and development.

Pharmacognosy

- Pharmacognosy deals with the study of natural products and their metabolites, which paves the way into drug discovery and investigation of the mechanism of action of ancient medicines.

Pharmaceutical biotechnology

- Pharmaceutical biotechnology is at the core of most methodologies and is now in use for drug discovery and development of both biologics and small molecules.

Pharmaceutical chemistry

- Knowing the therapeutic effects of natural products and biologics, pharmaceutical chemistry facilitates structure-based drug discovery by targeting receptors, enzymes and ion channels.

Pharmaceutical analysis

- Pharmaceutical analysis deals with the identification, characterization and quantification of substances in raw materials, dosage forms and biological samples.

Pharmacology

- In pharmacology, the cellular and molecular mechanisms of new chemical entities/repurposed drugs are determined by using *in vitro*, *ex vivo* and *in vivo* studies.

Pharmaceutics & pharmaceutical engineering

- Designing, imparting stability, and targeted delivery of drug formulations are under the control of pharmaceutics or pharmaceutical engineering.

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