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Review article

DRUG DISCOVERY PROCESS: CURRENT STATUS

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Abstract

Background: *Drug discovery has its roots right from the early 19th century when natural products from various parts of a plant were known to exert positive effect on mankind based upon the principles of traditional healing and religious belief. Early drug discoveries used to rely much upon serendipity.*
Objective: *The purpose of this article is to outline the current status of drug discovery and its accomplishments after the introduction of modern scientific approaches.*
Methods: *The data was gathered after extensive literature study from various scientific journals and books accessible from electronic databases like Pub Med, Science Direct, Web of Science, Google Scholar, etc.*
Results and Discussion: *Medicinal chemists have played a remarkable role in bringing the drug discovery process to a new extent with modern spectrometric and chromatographic techniques. Natural product discovery is now possible with less time and expense as compared to the ancient times. However, after the massive pandemic has hit the country with a big blow the trends in the discovery of a new drug processes are seriously affected where pharmaceutical industries have played a pivotal role in bringing this to balance. Today, drug discovery can be carried on with less laborious way than before due to technological advancements in the field of medicinal chemistry.*
Conclusion: *Today, the whole scenario has taken a drastic leap due to the introduction of advanced scientific tools, software, and molecular modeling approaches including receptor-ligand based pharmacology, computer-aided techniques, and optimized screening methods that have helped to carry out the process more tactfully.*

Keywords: Drug discovery, Medicinal chemist, Molecular modelling, Natural products

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Introduction

Humanity has been in an interminable combat with diseases since the ancient times. While many discoveries and modifications have been made to a drug substance to improve its reliability to be used as a medicine to cure, still many challenges come in our way that hinders its effectiveness to be considered as a "successful "discovery[1]. Drug discovery is a massive process that leads to a new molecule being developed or introduced into the market for the benefit of the society. Briefly, a drug development process requires around 12-15 years for a drug molecule to be fully established into a new drug candidate[2].We can imagine, how long this time is and how much expenditure it must meet to finally reach the market. It takes more than 1$ billion to carry out this drug discovery process from scratch to a potential drug candidate[3]. Drug discovery progresses through various stages of drug development, from initial hit identification through pre-clinical and clinical studies to FDA review and finally post-marketing surveillance in order to check the effectiveness of the drug after it reaches a large-scale of population [4]. In this review, we will discuss each and individual every stages in details to have an in-depth idea on the domain and its current status. The complex journey of a drug through this whole process made it necessary for the researchers to undergo fully fledged pre-clinical studies, Investigational new drug (IND) applications, and clinical testing experiments before a drug can finally get marketing approval from FDA [5]. Researchers can dig into new insights for a disease etiology or progression that can enlighten novel pathway for which a new drug can be intervened [4]. Alternatively, many companies conduct a large-scale trial process to identify the compound of interest. In fact, calculated risks and smart investments at this particular point of time can eventually increase the chances of triumph for a new candidate [4, 6]. Today, the process of drug discovery travels all the way right from the *in silico* screening of hits using computer simulation software through hit identification, optimization, and molecular tests to minimize side effects, till the development of a new drug candidate [7]. The considerable speed at which drug discovery has gained pace in recent years is due to the continuous development in medicinal chemistry, computer-aided drug designing software, molecular biology, and organic chemistry [1]. The thorough understanding of disease pathophysiology by molecular biological disciplines also assisted in the process of discovery and development [8]. Previously, drug discoveries were the results of serendipity as well as continuous trial and error experimental process, which could finally derive into an unknown substance, later came to be known as a drug. The discovery of penicillin is one such example [9,10]. It was only during the 1980s when the drug discoveries deliberately started coming into the pipeline. The medicinal chemists have played a very important role in this regard, by selecting appropriate compounds for biological evaluation, which if found to be capable enough could be

considered as a lead molecule [11]. These compounds are then studied for their structure-activity relationship on the basis of *in vitro* and *in vivo* evaluation parameters so as to produce analogous compounds relevant to the lead molecule [11]. From 1980 to the present, the technological development in high throughput virtual screening, combinatorial chemistry and molecular docking has entirely changed the previous topography [2, 4, 5]. This requires extreme expertise in the interdisciplinary domain, confirmatory evidence for each and every data generated and a huge resources including man power. Also, the clinical data for reporting the safety and efficacy on human subjects is far more complex and time taking [12, 13]. Despite the incessant development in this field, the percentage of molecules being considered as a drug is very few. Moreover, the regulatory agencies nowadays require adequate specifics and clarifications for the data generated and the guidelines have been made much more stringent than before [13]. The ultimate aim of drug discovery is to bring the safer and more efficacious drug into the market within a short time period after extensive medical evaluation [14, 15].

Drug discovery consists of 5 major steps, including a few subdivisions in each of them:

1. Pre discovery
2. Pre-clinical research
3. Clinical research
4. Post-marketing surveillance

Today Indian pharmaceutical industry is ranked 3rd in terms of generic discovery of drugs in a large volume due to development in the field of chemistry and collaborative research and development with other drug agencies for multi-disciplinary outcomes. The following phases of drug discovery need to be understood in detail in order to know the drug discovery and development process [16].

Pre discovery

Historically, discovery used to happen by chance or by adopting certain exhaustive or random screening approaches for identifying active ingredients from traditional medicinal plant or medicines, followed by applying the principles of classical pharmacology to assess any therapeutic potential of the selected candidate. Nowadays, the steps include identifying few potential molecule or hits, through screening approach, advanced medicinal chemistry to evaluate the parameters, selecting the most potent molecular lead, and finally the optimization of lead to minimize or obliterate the side effects, if any [17, 18].

Identification and validation of the target

The goal of identifying a target is to find out any therapeutic constituent, a particle, protein or a gene that is responsible for showing some activity for a disease. Provided it must be potential, safe, recognizable, and novel and should have any previous history for malicious events. Thus a target must be "druggable" [19].
Target validation involves the verification of the agent to demonstrate its ability to show suitable pharmacological effect for a certain specified range which is otherwise considered as the therapeutic window. To validate targets, specific techniques are used such as cell based models, interaction of proteins, disease association genetics, expression profile, functional gene analysis, *in vitro*/*in vivo* genetic manipulation, biomarkers and chemical genomics.[20] Usually, the validation process takes 3-6 months or even more depending on the research and resources available [19, 20].

Identification of hit

Through compound screening tools like high throughput screening, assay development, robotics, Nuclear magnetic resonance (NMR) etc, various small molecules that show potential binding affinity for the receptor are screened out or selected. Virtual screening applies the law of molecular and quantum physics based on the available structural information to identify the hits. There are certain websites or agencies that offer service of screening out large compound libraries for academic or research purposes. This can narrow down the selection to few compounds amongst thousands or millions [21, 22].

Hit to lead discovery

This involves the identification and validation of lead compounds that can bind to a target with greater affinity and likeness, also the efficacy and selectivity is improved with better metabolic and chemical stability [22]. These compounds also show better results when subjected to *in vitro* and *in vivo* testing. The goal of this phase is to identify more promising candidates through limited optimization or structure-activity relationship (SAR) studies to enter into the last phase i.e., lead optimization [23].

Lead optimization

In this particular process, the lead compounds are synthesized into small analogues using the principles of organic chemistry and combinatorial chemistry. This is achieved by performing a thorough quantitative structure activity relationship (QSAR) studies that will improve the potency, minimize non specific binding or off target affinities and enhance pharmacokinetic and metabolic properties [7]. If a proper structural knowledge of the target is available, a structure based design approach can be employed to modify the molecules to fit into the active site of the receptor with more affinity and resemblance. This step ensures experimental evaluation and confirmation of ADMET properties through animal studies to reduce the associated side effects [24]. Thus, this can further narrow down the discovery process when a single lead compound has been obtained and optimized for its authenticity [25].

Pre-clinical research

When a suitable drug candidate has been found, the next step is to carry out *in vivo* testing of the drug candidates to ensure its safety and efficacy using pre-clinical studies. This particularly involves testing on laboratory animal species like rats, mice, rabbits, monkeys, and guinea pigs to test the appropriate benefits and mechanism of action, routes of administration, dosage, adverse drug events, non-targeted interactions, comparison of efficacy, etc [26]. It ensures that the drug is sufficiently safe to be tested on humans; it enlightens the clarity if there is any effect of the selected drug on gender, particular age group, race, or other ethnic groups. Thus, pre-clinical research can be done to know the toxicity, pharmacokinetics and efficacy of a new drug entity before experimenting on humans [26, 27]. It gives a preliminary idea regarding the behavior of drug.

***In vitro, in vivo* and *ex-vivo* experiments**

In-vitro experiment is conducted on a laboratory mimicking environment for body physiological processes to know the original fate of the drug after it enters the human body [28]. *In vivo* are the experimental procedures conducted directly on an animal models to track their behaviour and response while the *ex vivo* involves collecting animal tissues or living cells or organs from an organism to check the effect of the drug e.g. – bioassays [29]. The drug delivery through oral, topical and parenteral route can be optimized with the pre clinical studies along with techniques to improve bioavailability [11]. Finally, a prepared drug formulation can be optimized before it enters into clinical research trials.

Clinical research

Before a drug is approved by the regulatory authority, it has to undergo extensive clinical trials that have been divided into few phases where each phase has its own relevance. Clinical trial is basically done to know whether a new drug in the verge of getting developed actually works or is it safe for the people [30]. This research can be helpful in estimating the disease diagnosis, extent of a disease, detection, safety and presence of any side effects related to the drug. For this purpose, healthy volunteers from various regions are selected and trial is conducted on them to answer the questions regarding the disease and the drug profile [31]. Before the clinical study is actually started, an application to conduct the research on a particular drug needs to be submitted to the Central Drugs Standard Control Organization (CDSCO) for approval [32]. This application is known as Investigational New Drug (IND) application which contains results from pre clinical studies, drug information, outline or study protocol to be carried out, and details about the research team who will be responsible for carrying out the trials [33].

Phase-0

This is done to know whether the drug does what it is expected to do. This also helps to save a huge amount of time and money. Here, micro-dosing of a drug is given, due to which risk factors are not there, and as a result, a drug can be tracked if it is reaching the site of action where it is desired, whether it is acting in a positive way and how the body reacts to it. Not every drug undergoes this trial, and it is conducted with a very limited no. of people for a short period of time [34, 35].

Phase-I

This is the first step in clinical trial where less than 100 volunteers are involved, may be around 20-80 people. Drug is given to check the safety dose and the maximum tolerable dose of a drug up to which it does not show any considerable side effect, here safety is the main concern and studying the response of a disease is not the main motive [36, 37].

Phase-II

Here the disease response is studied in around 25-100 volunteers and a comparative high dose is given as compared to the previous phase of trial. Efficacy is the main

concern of this study, if majority of the patients are showing response with minimal side effects, then the drug may proceed towards the phase-III clinical trial [38].

Phase-III

In this phase, comparative evaluation is done with the already established drug of similar category to assess the safety and efficacy of the developed drug. Here the volunteers are assigned to random groups and they himself including the physician are not aware of the specific group in which they are placed (double-blinded) [39]. It involves a large no. of people, among thousands from different geographical regions or countries and the tests are conducted for a long time period. Placebo groups are also included in this study to compare the standard and the test drug. If a patient experiences serious side effects which are less likely to be manageable, the treatment is stopped immediately and care as given [39, 40]. All the parameters for sample collection, treatment and particulars should be stringent and followed with proper skill and knowledge. When the study is completed and the new drug shows better potential than the standard or already established drug, then comes another application that needs to be submitted to the regulatory authority for approval purpose. This is known as New Drug Application (NDA). The team reviews and cross checks the results from the trials and decides whether to approve the drug for treatment. This step is considered to be very crucial as it decides the fate of a drug to reach where it is destined for [41].

Post marketing surveillance-Phase-IV

Is there still something remaining to be known about the drug? The answer to this question is yes [42]. Whenever a new drug candidate is introduced into the market, it contains a lot of questions that needs to be addressed. Whether it shows any rare side effect that was not observed before, does it improves the quality of life when taken for a long period of time, can all groups of people regardless of being wealthy or poor can have an access to this drug [43]. All this things needs to be questioned and answered at the same time which is only possible if the drug is reaching to the population affected with a cause. It can help future patients to increase the reliability on a drug. Thus, it is a post marketing surveillance study and marks the final process of clinical research after which the drug is free to be used without any hindrance [42, 43, 44].

Role of medicinal chemists in drug discovery

Medicinal chemists have been an enormous support in the upliftment of drug discovery process from last four decades not only in the enhancement of therapeutic potency of a drug but also to minimize the associated unwanted effects coming along with the drug [45, 46]. They validate the targets to optimize the synthesized or developed leads to show increased drug interaction. With the acquired knowledge of drug targets and ligands, medicinal chemists are able to formulate hypothesis for a new drug project and then characterize and purify the new drug candidate to progress into the subsequent stages of discovery [45]. Once the "hit" compound is selected, they try to synthesize compounds analogous to the proposed hit so as to study their structure activity relationship (SAR) to optimize the required drug activity [47]. The *in vivo* studies concerning pharmacokinetic parameters and to estimate no observed adverse effect level (NOAEL) along with potency and appropriate dosage for the drug are all the responsibilities to be carried on the shoulders of a medicinal chemist [48]. To work on the concepts of organic chemistry together with the biology of the drug-receptor relation requires thorough skills and expertise pertaining to specific tests to be conducted, specific software to be utilized, very specific protein to be studied, nucleic acid manners, etc. These are all the combined duties to be fulfilled by medicinal chemists [49]. Additionally, any similar drug in the market, if available, or otherwise discontinued or under trial phase of study should be pondered upon carefully by a medicinal chemist personnel [50]. The techniques to analyze a compound through various spectrometric and chromatographic tools such as UV Vis-spectroscopy, Infrared spectroscopy, Nuclear magnetic resonance (NMR) spectroscopy, column chromatography, Thin layer chromatography, High performance liquid chromatography for compound purification and quantification should be skilfully carried on [51, 52]. In fact, the development of receptor based pharmacology in the late 1980s and early 1990s has been an additional push in the drug discovery process [53]. Even though, the chemists still faces the difficulties during early drug discovery which they used to encounter 40 years ago, to deal with those challenges still the conventional principles like relevant data library, screening methods and QSAR studies are followed. Also, the data generated from the studies performed are well documented and tabulated in a digital as well printed format for ease of retrieval at the time of requirement [54]. Some heroic examples of recent drug discovery by collaborative efforts of a medicinal chemists and pharmacologists are listed below in Table 1.

Natural products in drug discovery

Drug discovery from natural products has always provided a thrust in the modern era of synthetic medicines. Since ancient times, natural products has shown considerable effects in treating various diseases or ailments such as cancer [55]. Although drug discovery from nature has always posed major challenges to isolate their active principle, ascertain its purity and elucidate the structural identity and optimization. Nonetheless, research based upon their chemistry and pharmacological activity has improved in a massive way in recent years due to technological and scientific advancements [56]. After the screening of crude plant specimen, further fractions that are to be evaluated are collected in order to isolate the active ingredient from the extract. With the development of metabolomics, this step can be accelerated tactfully with ease and less laborious work load [57]. Also, the development in chromatographic and spectroscopic tools such as NMR, liquid chromatography-mass spectrometry (LC-MS), LC-high resolution mass spectrometry (LC-HRMS), High performance thin layer chromatography (HPTLC) further stimulated the plant based research [51]. Thus, the plant based research has got a sudden boost in the verge of drug discovery and more technological advancements are already in place to improve the process to save time and expenses [58].

Software used in drug discovery

Drug discovery process has seen an extensive development after the introduction of modern software and related tools. These tools have not only contributed in saving the time and effort but has also improved the outcome of a research [59]. These tools have helped the pharmaceutical sectors to keep up the pace and be competitive in the market by increasing their productivity both in analytical as well as medicinal domain. One such prominent development is the discovery of ChemDraw, a drawing tool that helps chemists across the globe to draw the structure of a compound in a very uncomplicated and straightforward approach [60]. It has numerous key features ensemble on it, one such being the provision of detecting the IUPAC names of the distinguished structures in a matter of seconds including its physical and chemical properties etc. Other such examples are AutoDock, Schrodinger, Biovia discovery studio, DDD plus, mapcheck etc [61-64]. These applications has not only helped the researchers in saving their valuable time and effort but has also ensured better reliability and reproducibility of results. A very important aspect of data analysis or interpretation is the art of capturing the image in an incredible and subtle way so as to make it suitable for publishing requirements. The software can help us achieve the same by increasing the quality

and impact of the generated image [65, 66]. Table 2 enlists some of the common software being utilized in the process of drug discovery. A combined illustrations and enumerations of the entire drug related software is beyond the scope of this article

Post Pandemic Status

Apart from a numerous challenges that a researcher comes across during the discovery of a drug, Various unexpected circumstances can come our way that can further delay the process, the dramatic pandemic COVID-19 is one such instance [67]. It has substantially affected the whole world for last few years due to which the entire scientific research and development process are still in the verge of difficulties. The clinical trials for new drugs have been detained or postponed, economic demand-supply chain got disturbed, innovation could not meet the standards due to unavailability of resources etc. [68]. Overall, it posed a serious threat to carry out a smooth functioning of drug research involving pre-clinical and clinical trials.[67] However, the fact couldn't be denied that new vaccines to tackle this catastrophe got developed in a very short span of time with the continuous efforts of healthcare professionals and researchers from various fields.[69] But the challenge lies in further inventive approaches to develop certain antibodies and peptides that could assist to face the future scenario as the virus being constantly replicating and modifying its nature suggesting that it can escape or become resistant to the previously adopted strategy [68, 69].Thus, a huge no. of scientists, individual researchers, pharmaceutical industries are already in the verge of developing new target agents to prevent or counter the pandemic virus due to which the therapeutic drug discovery process for development of other categories of disease treating agent got a bit slackened [70]. So the barriers in drug discovery post pandemic need to be addressed taking into consideration the global impact in past, present and future. Currently, drug discovery is again gaining that flow due to the establishment of new biotechnological and pharmaceutical research centres dedicated to COVID-19 only where it collaborates with multiple disciplinary areas to make sure that it doesn't hinder the process [71].

Conclusion

Drug discovery and development has seen diversified circumstances right from the early 19th century till today. In ancient times, drug discovery used to rely upon traditional system and remedies including serendipitous discoveries, one such example being penicillin [72]. This period marked the beginning or the first phase of drug discovery. Indian civilizations are known for the traditional system of medicines and its utilization to treat several ailments based on the principles of

religious belief and spiritual healing [73].The traditional system is based upon the use of roots, herbs and several other significant parts of a plant known to cure disease, some of the well known candidates including *Curcuma longa*, *Bacopa monierri*, *Coleus forskohlii* etc. [16]. In the second phase of drug discovery, drug structures, their mechanisms, related pharmacology began to be known which resulted in a drastic development due to the incorporations of molecular modeling and combinatorial chemistry approaches [74].Antibiotics were discovered during this phase and the knowledge regarding DNA, RNA, recombinant technology and molecular biology began to be known. The third phase of drug discovery can be traced with the development of biopharmaceutical agents approved by regulatory authorities all around the globe [74].Nowadays, drugs need to be designed and evaluated from a broad set of library containing similar analogs. This will allow the screening of a specific drug to be utilized for research. This is further followed by an optimization step to improve the efficacy of the candidate drug incorporating mechanistic profile of safety and reliability with minimum or no adverse effects [75].The lead molecule than enters the pre clinical and clinical stages to estimate the dose level, toxicity and therapeutic activity before they could ultimately reach to the market. This whole process will be incomplete until the "new chemical entity" gets approval from the standard regulatory bodies to be able to known as a newly discovered "drug" [76].In context to this entire process, it is important to mention that how greatly the medicinal chemists have played a very important role in the success of drug development using advanced scientific software and various novel strategies [11, 17, 77].

After the sudden appearance of global pandemic, the whole healthcare system has experienced several highs and lows including uncertainties and numerous complications towards the drug discovery and development [78, 79].Therefore, continuous efforts of medicinal chemists and pharma companies are necessary to remain on a par with recent developments to aid in drug discovery [78-80].

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Conflict of Interest

The authors declare no conflicting interests.

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Table 1: Recently approved drugs by Food and drug administration (FDA) [88-90]

S. No	Drug	Use	Year of discovery
1	Ebanga	Ebola	2020
2	Voquezna	*H. pylori* infection	2022
3	Cibinqo	Atopic dermatitis	2022
4	Vtama	Plaque psoriasis	2022
5	Quvivic	Insomnia	2022
6	Margenza	HER2+ breast cancer	2020
7	Pyrukynd	Haemolytic anaemia	2022
8	Vyvgart	Myasthenia gravis	2021
9	Quilipta	Episodic migraines	2021
10	Aduhelm	Alzheimer's disease	2021

Table 2: List of most commonly used software in drug discovery

S. No.	Name of the software	Original Use	Other use	References
1	ChemOffice	To draw chemical structures	Physical, chemical properties of a compound	[60]
2	AutoDock	Structure based drug design	Virtual screening, molecular docking	[81]
3	Schrodinger	Molecular modelling, simulation, dynamics	Protein structure analysis	[82]
4	ArgusLab	Drug designing	Molecular docking	[83]
5	Design-Expert	Optimization and screening of experiments	Validation, response evaluation of experiments	[62]
6	QSAR-co	To develop QSAR models	Screening and prediction of developed models	[84]
7	GraphPad prism	Statistical analysis of data	Comparison of significance of data	[85]
8	PyMol	For compound visualization	Pharmacophore modeling	[65]
9	Gromacs	Molecular dynamics	Simulation of amino acids, proteins etc.	[63]
10	Unipept	Metaproteomics study	Peptide characterization and analysis	[66]
11	Accord	Cheminformatics	Storage and analysis of chemical structures	[61]
12	Jaguar	Quantum chemistry	Interpretation of	[86]

		and calculations	spectrophotometric results	
13	Gold	Flexible docking	Covalent docking, pose prediction	[64]
14	SwissADME	Pharmacokinetics	Drug likeness, physicochemical evaluation	[87]
15	Ethowatcher	Behavioural analysis of animals	Physiological changes in laboratory animals	[59]

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