CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES

SJIF Impact Factor: 7.187

http://doi.org/10.5281/zenodo.4371781

Avalable online at: http://www.iajps.com *Review Article*

REVIEW OF DRUG DISCOVERY PROCESS

Padmaja Devi M.S.*, Vaishna.V.V., Prasobh G.R. and Sheeja Rekha A.G.

[1] *Associate professor, Department of Pharmaceutical Chemistry & Analysis, Sreekrishna College of Pharmacy and Research Centre, Parassala, Tvpm Dist, Kerala.*

Article Received: October 2020 **Accepted:** November 2020 **Published:** December 2020

Abstract:

The objective of this paper is to study the drug discovery process from lead molecules.

In the past most drugs have been discovered either by identifying the active ingredient from traditional remedies or by serendipitous discovery.

Key words: *Target identification, Lead discovery, Drug design, Drug synthesis*

Corresponding author:

Padmaja Devi M.S.,

Associate professor, Department of Pharmaceutical Chemistry & Analysis, Sreekrishna College of Pharmacy and Research Centre, Parassala, Tvpm Dist, Kerala.

QR code

Please cite this article in press Padmaja Devi M.S.et al, ***Review Of Drug Discovery Process.,*** *Indo Am. J. P. Sci, 2020; 07(12).*

INTRODUCTION:

Drug discovery is a multifaceted process, which involves identification of a drug chemical therapeutically useful in treating and management of a disease condition. Typically, researchers find out new rugs through new visions into a disease process that permit investigator to design a medicine to stopover or contrary the effects of the disease.

[1] The process of drug discovery includes the identification of drug candidates, synthesis, characterization, screening, and assays for therapeutic efficacy. When a molecule avails its satisfactory results in these investigations, it will commence the process of drug development subsequent to clinical trials. Drug discoveryand development is an expensive process due to the high budgets of R&D and clinical trials. It takes almost 12-15 years to develop a single new drug molecule from the time it is discovered when it is available in market for treating patients.

[2] The average cost for research and development for each efficacious drug is likely to be $900 million to $2 billion. This figure includes the cost of the thousands of failures: For every 5,000-10,000 compounds that enter the investigation and development pipeline, ultimately only one attains approval. These statistics challenge imagination, but a brief understanding of the R&D process can explain why so many compounds don‘t make it and why it takes such a large, lengthy effort to get one medicine to patients.[3] The Success requires immense resources the best scientific and logical minds, highly sophisticated laboratory and technology; and multifaceted project management. It also takes persistence and good fortune.[4] Eventually, the process of drug discovery brings hope, faith and relief to billions of patients.[5]

Stages of drug discovery and development include:

- Target identification
- Target validation lead identification
- lead optimization
- Product characterization
- Formulation and development
- Preclinical research
- Investigational New Drug
- Clinical trials
- New Drug Application
- Approval

Figure 1: Stages of drug discovery and development process

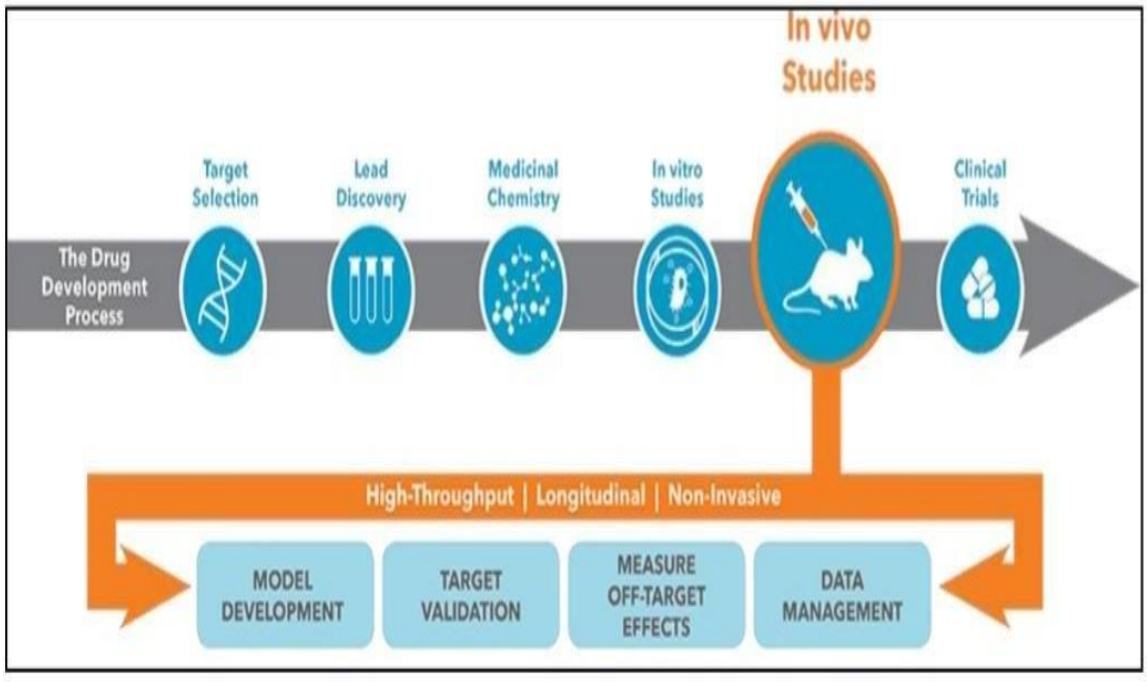


Figure 1: Stages of drug discovery and development process

Target identification:
The first step in the discovery of a drug is identification of the biological origin of a disease, and the potential targets for intervention. Target identification starts with isolating the function of a possible therapeutic target (gene/nucleic acid/protein) and its role in the disease. [6] Identification of the target is followed by characterization of the molecular mechanisms addressed by the target. An ideal target should be efficacious, safe, meet clinical and commercial requirements and be ‗druggable'. The techniques used for target identification may be based on principles of molecular biology, biochemistry, genetics, biophysics, or other disciplines.[7]

Approaches:
Data mining using bioinformatics identifying, selecting and prioritizing potential disease targets Genetic association
genetic polymorphism and connection with the disease Expression profile changes in mRNA/protein level Pathway and phenotypic analysis

In vitro cell-based mechanistic studies Functional screening knockdown, knockout or using target specific tools [8]

Target Validation:
Target validation is the process by which the expected molecular target – for example gene, protein or nucleic acid of a small molecule is certified. Target validation includes: determining the structure activity relationship(SAR of analogs of the small molecule; generating a drug-resistant mutant of the presumed target; knockdown or over expression of the presumed target; and monitoring the known signaling systems downstream of the presumed target.

Target validation is the process of demonstrating the functional role of the identified target in the disease phenotype. Whilst the validation of a drug's efficacy and toxicity in numerous disease-relevant cell models and animal models is extremely valuable – the ultimate test is whetherthe drug works in a clinical setting.[10]Target validation can be broken

Identification of Lead:
A chemical lead is defined as a synthetically stable, feasible, and drug like molecule active in primary and secondary assays with acceptable specificity, affinity and selectivity forthe target receptor. This requires definition of the structure activity relationship as well as determination of synthetic feasibi lity and preliminary evidence of in vivo efficacy and target engagement.

Lead Optimization:
Lead optimization is the process by which a drug candidate is designed after an initial lead compound is identified. The process involves iterative series of synthesis and characterization of a potential drug to build up a representation of in what way chemical structure and activity are related in terms of interactions with its targets and its metabolism.

Product Characterization:
When any new drug molecule shows a promising therapeutic activity, then the molecule is characterized by its size, shape, strength, weakness, use, toxicity, and biological activity. Early stages of pharmacological studies are helpful to characterize the mechanism of action of the compound.

Formulation and Development:
Pharmaceutical formulation is a stage of drug development during which the physicochemical properties of active pharmaceutical ingredients (APIs) are characterized to produce a bioavailable, stable and optimal dosage form for a specific administration route.

Preclinical Testing:
Pre-clinical research in drug development process involves evaluation of drug's safety and efficacy in animal species that conclude to prospective human outcome. The pre-clinical trials also have to acquire approval by corresponding regulatory authorities. The regulatory authorities must ensure that trials are conducted in safe and ethical way and would give approval for only those drugs which are confirm to be safe and effective. ICH has established a basic guideline for technical necessities of acceptable preclinical drug developme

The Investigational New Drug Process (IND):

Drug developers must file an Investigational New Drug application to FDA before commencement clinical research.[20] In the IND application, developers must include:

- Preclinical and toxicity study data
- Drug manufacturing information
- Clinical research protocols for studies to be conducted
- Previous clinical research data (if any)
- Information about the investigator/ developer [21]

Clinical Research

Clinical trials are conducted in people (volunteer)and intended to answer specific questions about the safety and efficacy of drugs, vaccines, other therapies, or new methods of using current treatments. Clinical trials follow a specific study protocol that is designed by the researcher or investigator or manufacturer clinical study, they will consider what they want to complete for each of the different Clinical Research Phases and starts the Investigational New Drug Process (IND), a process they must go through before clinical research begins. Before a clinical trial begins, researchers review prior information about the drug to develop research questions and objectives.[22] Then, they decide:

- Selection criteria for participants
- Number of people take part of the study
- Duration of study
- Dose and route of administration of dosage form
- Assessment of parameters
- Data collection and analysis

New Drug Application:

A New Drug Application (NDA) expresses the full story of adrug molecule. Its purpose is to verify that a drug is safe and effective for its proposed use in the people studied. A drug
developer must include all about a drug starting from preclinical data to Phase 3 trial datain the NDA. Developers must include reports on all studies, data, and analysis.Beside with clinical trial outcomes, developers must include:

- Proposed labeling
- Safety updates
- Drug abuse information
- Patent information

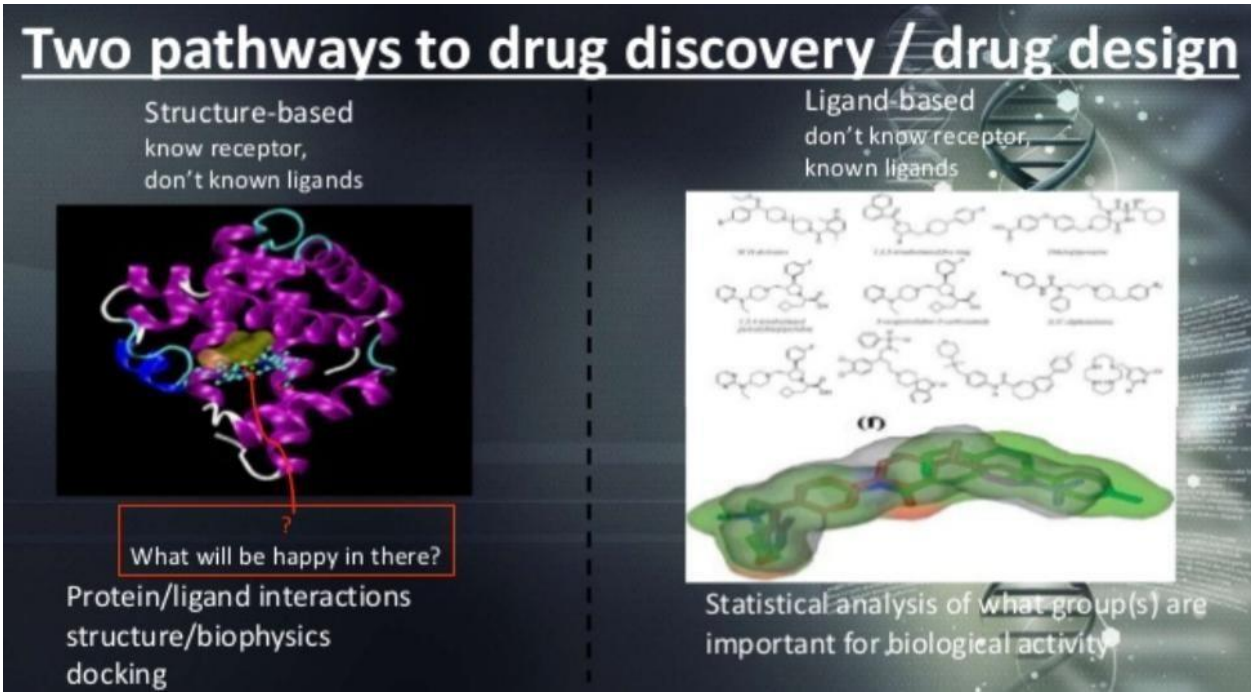
OBJECTIVES OF DRUG DESIGN:

- To identity how to relate chemical structure to biological activity.
- To understand how to conduct a structure activity analysis.
- Identify atleast one molecule with improved action in Over an existing drug with same target.
- Find & select the target disease in the human body.
- Search & choose the best drug candidate.
- Conduct computerized drug design simulation.
- To improve the activity & properties of the lead compound.
- To improve the binding interaction between a drug & its target, which will increase the activity & also reduce the side-effects if it increased interaction lead to increased selectivity between different target.

IN-SILICO DRUG DESIGN:

In-silico is an expression used to mean “performed on computer or via computer simulation.” In-silico drug designing as the identification of the drug target molecule by employing bioinformatics tools.

Types of In-silico Drug Design:



SELECTION OF LEAD MOLECULE FROM NATURAL PRODUCTS:

Lead Identification:

The rational approach of lead discovery (concerned with the site of mechanism of action at cellular, molecular as well as electronic level the 3 dimentional structures of receptors and its compliment drug to be) is designed is significant to the identification of lead design which in turn is considered as the heart of the drug design.

Methods/Sources of drug

- The rational approach of lead discovery(concerned with the site of mechanism of action at cellular,molecular as well as electronic levels,the three dimensional structures of receptor and it's complement drug to be designed) is significant in the identification of lead nucleus which in turn is considered as the heart of the drug design.
- Methods/sources for identification of lead compound
- From natural source
- Plants are considered as the primary and oldest source of drugs.Several drugs are obtained naturally from plants.
- Example:Morphine from opium act as an analgesic,atropine from belladona act as parasympathetic blocker,digoxin and digitalis from foxglove plant act as cardiac stimulants, d-tubocurarine from curare plant act as a skeletal muscle relaxant etc.
- Since plant are an important source for several potential new drugs,these are regularly screened for newer active constituents.

Modified percolation:

- The conventional percolation process is modified to include evaporation for the production of more concentrated products,especially when the solvent is dilute alcohol
- In simple percolation
- Drug—imbibition—maceration—percolation and collect the percolate
- In conventional percolation
- Drug—imbibition—maceration—percolation and collect the 1000ml of percolate
- .Maceration—percolation and collect the 1000ml of percolate
- The process is continued in case the drug is not completely exhausted.

Hot continuous extraction(soxhlet):

- In this method the finely ground crude drug is placed in a porous bag or "thrumble" made of strong filter
- paper,of the Soxhlet apparatus.
- The extracting solvent flask is heated,and it's vapors condense in condenser.The condensed extracting drips
- into the thrumble containing the crude drug,and extracts it by contact.
- When the level of liquid in chamber rises to the top of siphon tube,the liquid contents of chamber siphon into flask.This process is continuous and is carried out until a drop of solvent from the siphon tube does not leave residue when evaporated.
- The advantage of this method,compared to previously described methods,is that large amounts of drugs can be extracted with a much smaller quantity of solvent.

Aquoeus alcoholic extraction by fermentation:

- It involves soaking the crude drug,in the form of either a powder or a decoction for a specified period of time,during which it undergoes fermentation and generates alcohol in situ;this facilitates the extraction of the active constituents contained in the plant material.
- The alcohol thus generated also serves as a preservatives .
- Some examples of such preparations are Karpurasava,kanakasava,dasmularista.

Counter-Current Extraction

- In counter-current extraction(CCE),wet raw material is pulverized and produce a fine slurry.
- Here the material to be extracted is moved in one direction within a cylindrical extractor where it comes in contact with extraction solvent.
- The further the starting material moved,the more concentrated the extract becomes.
- Complete extraction is thus possible when the quantities of solvent and material and their flow rates are optimized.
- Finally,sufficiently concentrated extract comes out at one end of the extractor while the Marc falls out from the other end.

Advantages:

Smaller volume of solvent as compared to other methods like maceration,decoction,percolation.

CCE is commonly done at room temperature,which spares the thermolabile constituents from exposure to heat which is employed in most other techniques.

As the pulverization of the drug is done under wet conditions,the heat generated during comminution is neutralized by water.This again spares the thermo labile constituents from exposure to heat.

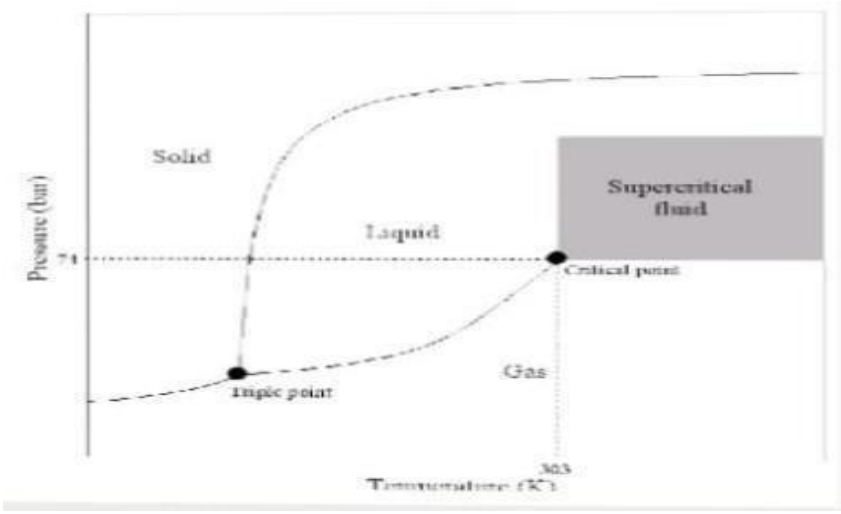
The extraction procedure has been rated to be more efficient and effective than continuous hot extraction.

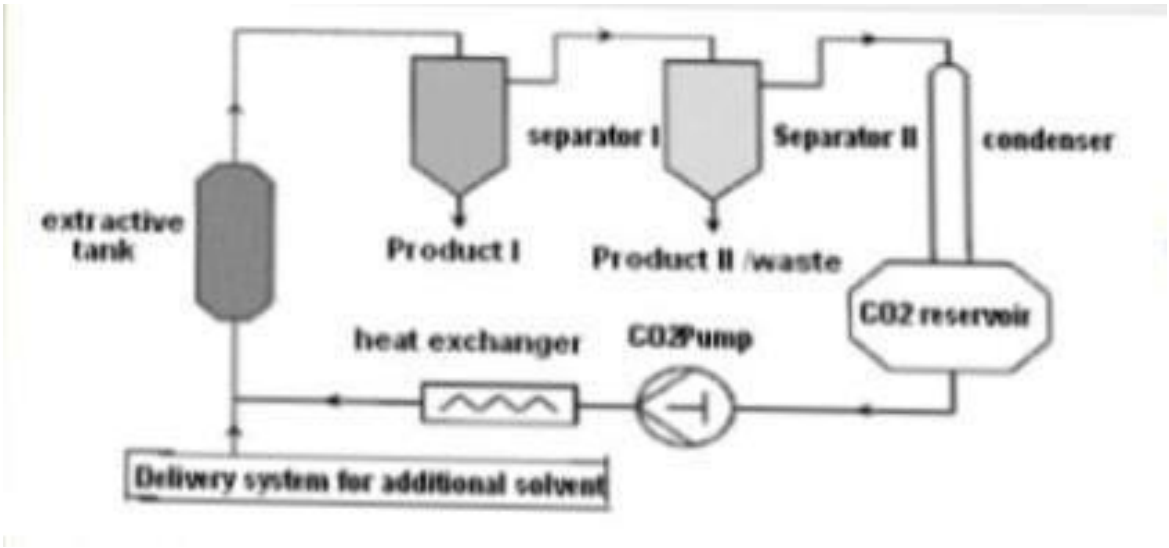
Ultrasound Extraction(sonication)

- The procedure involves the use of ultrasound with requencies ranging from 20kHz;this increases the permeability of cell walls and produce cavitation.
- The process is useful in some cases,like extraction of rauwolfia root,it's large scale application is
- limited due to the higher costs.

Disadvantage:

- The deleterious effect of ultrasound energy (more than 20kHz) on the active constituents of medicinal plants through formation of free radicals and consequently undesirable changes in the drug molecules.
- Supercritical fluid extraction
- The critical point represents the highest temperature and pressure at which the substance can exist as a vapour and liquid in equilibrium.The phenomenon can be easily explained with reference to the phase diagram for pure carbon dioxide.





Advantages:

- The extraction of constituents at low temperature,which strictly avoids damage from heat and some organic solvents.
- No solvent residues
- Environmentally friendly extraction procedure
- The main drawback is the time of extraction,which is usually long.in fact in some cases,it can take as much as 24 hours .with normal fluids ,extraction can be speeded up by mechanical shaking,but this presents problems when using super-critical fluids,which limits industrial use.

REFERENCES:

1. Text book of drug design by Patrick
2..Text book of medicinal chemistry by BURGER